COMPARISON OF AUTONOMIC FUNCTION CHANGES BY FIXED PRESSURE VERSUS AUTO ADJUSTING CONTINUOUS POSITIVE AIRWAY PRESSURE IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

THESIS SUBMITTED TO THE FACULTY OF

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, BHOPAL

FOR THE AWARD OF THE DEGREE DM
IN THE SUBJECT OF
PULMONARY, CRITICAL CARE AND SLEEP MEDICINE

BY
Dr. S. ANUSHA RAO
REG NO: APMC/FMR/79412

UNDER THE GUIDANCE OF
Dr. ABHISHEK GOYAL
Former Additional Professor
Department of Pulmonary Medicine,
AIIMS Bhopal

OCT 2024

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, BHOPAL

UNDERTAKING

I, **Dr. S Anusha Rao**, DM scholar registered in the batch January 2022, vide registration no.**2200033M03S60003,** hereby declare that the data submitted for my DM thesis belongs to me and is original. I also certify that the work was done by me to carry out this study.

The Institute shall not be responsible for any dispute or any conflict of interest that may arise out of this thesis at any stage.

Name of the student: Dr. S Anusha Rao

Guide:

Dr. Abhishek Goyal

Additional Professor (Former)

Department of Pulmonary medicine

All India Institute of Medical Sciences, Bhopal

Dr. Abhishek Goyal
MD (Medicine)
DM (Pulmonary & Critical Care Medicine-
PGIMER, Chandigarh)
Additional Professor &
Pulmonary Medicine
AIIMS, Bhopal

Place: Bhopal

Date: 14-10-2024

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, BHOPAL

UNDERTAKING

I, **Dr. S Anusha Rao** DM scholar registered in the batch January 2022, vide registration no.**2200033M03S60003,** hereby declare that the data submitted for my DM thesis belongs to me and is original. I also certify that the work was done by me to carry out this study.

The Institute shall not be responsible for any dispute or any conflict of interest that may arise out of this thesis at any stage.

Name of the student: Dr. S Anusha Rao

Prof. (Dr.) Alkesh K. Khurana
Reg.No. PMC-.34092 M.D., DNB
Professor
Deptt. of Pulmonary Medicine
AIIMS, Bhopal - 462020

Head of the department

Dr. Alkesh Kumar Khurana

Professor and Head

Department of Pulmonary medicine

AIIMS, Bhopal

Place: Bhopal

Date: 14-10-2024

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, BHOPAL

CERTIFICATE

This is to certify that the thesis entitled "**Comparison of autonomic function changes by fixed pressure versus auto adjusting continuous positive airway pressure in patients with Obstructive Sleep Apnea**" is a bonafide and genuine research carried out by **Dr. S Anusha Rao** under the guidance and direct supervision for the award of DM degree.

Name of the Guide and Designation:

Dr. Abhishek Goyal

Additional Professor (Former)

Department of Pulmonary medicine

Dr. Abhishek Goyal
MD (Medicine)
DM (Pulmonary & Critical Care Medicine-PGIMER, Chandigarh)
Additional Professor &
Pulmonary Medicine
AIIMS, Bhopal

Name of the Co-Guide and Designation:

Dr. Alkesh Kumar Khurana

Professor and Head

Department of Pulmonary medicine

Prof. (Dr.) Alkesh K. Khurana M.D., DNB
Reg.No. PMC-.34092
Professor
Deptt. of Pulmonary Medicine
AIIMS, Bhopal - 462020

Dr. Ruchi Singh

Associate Professor

Department of Physiology

डॉ.रुचि सिंह / Dr. RUCHI SINGH
Reg.No.29682 MBBS, M.D.(Physiology)
प्राध्यापक / Professor
शरीरक्रिया विज्ञान विभाग / Deptt. of Physiology
अखिल भारतीय आयुर्विज्ञान संस्थान भोपाल-462020
All India Institute of Medical Sciences Bhopal-462020

Place: Bhopal

Date: 14-10-2024

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, BHOPAL

DECLARATION

I hereby declare that the thesis entitled "**Comparison of autonomic function changes by fixed pressure versus auto adjusting continuous positive airway pressure in patients with Obstructive Sleep Apnea**" is a bonafide and original work carried out by me under the guidance of **Dr. Abhishek Goyal,** Additional Professor, Department of Pulmonary medicine **Dr. Alkesh Kumar Khurana,** Professor and Head, Department of Pulmonary medicine and **Dr. Ruchi Singh,** Associate Professor, Department of Physiology. The thesis or any part thereof has not formed the basis for the award of any degree/fellowship or similar title to any candidate of any university to the best of my knowledge.

Dr. S Anusha Rao
Academic Senior Resident

Place: Bhopal
Date: 14-10-2024

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, BHOPAL

CERTIFICATE

This is to certify that the thesis entitled "**Comparison of autonomic function changes by fixed pressure versus auto adjusting continuous positive airway pressure in patients with Obstructive Sleep Apnea**" is a bonafide and genuine research carried out by **Dr. S Anusha Rao** under the guidance and direct supervision of **Dr. Abhishek Goyal,** Additional Professor, Department of Pulmonary medicine.

Dr. Abhishek Goyal
Former Additional Professor
Department of Pulmonary medicine
All India Institute of Medical Sciences, Bhopal

Dr. Abhishek Goyal
MD (Medicine)
DM (Pulmonary & Critical Care Medicine)
PGIMER, Chandigarh)
Additional Professor &
Pulmonary Medicine
AIIMS, Bhopal

Place: Bhopal

Date: 14-10-2024

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, BHOPAL

CERTIFICATE

This is to certify that the thesis entitled "**Comparison of autonomic function changes by fixed pressure versus auto adjusting continuous positive airway pressure in patients with Obstructive Sleep Apnea**" is a bonafide and genuine research carried out by **Dr. S Anusha Rao** under the guidance and direct supervision of **Guide Dr. Abhishek Goyal,** Additional Professor, Department of Pulmonary medicine, **Co-guide Dr. Alkesh Kumar Khurana,** Professor and Head, Department of Pulmonary medicine, and **Co-guide Dr. Ruchi Singh,** Associate Professor, Department of Physiology in AIIMS Bhopal.

Rajnish Joshi

DEAN (ACADEMICS)
AIIMS, BHOPAL

Place: Bhopal

Date: 14-10-2024

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, BHOPAL

COPYRIGHT DECLARATION

We hereby declare that All India Institute of Medical Sciences, Bhopal, shall have all the rights to preserve, use and disseminate this thesis in print or electronic format for academic/research purpose.

Dr. S Anusha Rao

Academic Senior Resident

Name of the Guide and Designation:

Dr. Abhishek Goyal

Additional Professor (Former)

Department of Pulmonary medicine

All India Institute of Medical Sciences, Bhopal

Dr. Abhishek Goyal
MD (Medicine)
DM (Pulmonary & Critical Care Medicine-
PGIMER, Chandigarh)
Additional Professor &
Pulmonary Medicine
AIIMS, Bhopal

Name of the Co-Guide and Designation:

Dr. Alkesh Kumar Khurana

Professor and Head

Department of Pulmonary medicine

Prof. (Dr.) Alkesh K. Khurana M.D., DNB
Reg.No. PMC-34092
Professor
Deptt. of Pulmonary Medicine
AIIMS, Bhopal - 462020

Dr. Ruchi Singh

Associate Professor

Department of Physiology

All India Institute of Medical Sciences, Bhopal

डॉ.रुचि सिंह / Dr.RUCHI SINGH
Reg.No.29682 MBBS, M.D.(Physiology)
प्राध्यापक / Professor
शरीरक्रिया विज्ञान विभाग / Deptt. of Physiology
अखिल भारतीय आयुर्विज्ञान संस्थान भोपाल-462020
All India Institute of Medical Sciences Bhopal-462020

Place: Bhopal

Date: 14-10-2024

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, BHOPAL

Saket Nagar, Bhopal – 462020 (M.P)

Institutional Human Ethics Committee- PostGraduate Research (IHEC-PGR)

www.aiimsbhopal.edu.in Email: ihecpgr@aiimsbhopal.edu.in

Ref Number: IHEC-PGR/2022DM-MCh/Jan/07 **Date:** 12th September 2022

Letter of Permission

Student Investigator: **Dr S Anusha Rao** **Pulmonary Critical Care and Sleep Medicine**	**Guide:** **Dr Abhishek Goyal** **Pulmonary Critical Care and Sleep Medicine**

AIIMS, Bhopal Institutional Human Ethics Committee- Post Graduate Research (IHEC-PGR) in its 6th meeting held on 17th August 2022 discussed your proposal titled **"Comparison of autonomic function changes by fixed pressure versus auto adjusting continuous positive airway pressure treatments in patients with Obstructive Sleep Apnea"** and evaluated it for suitability for your dissertation as required for fulfilment of DM/M.Ch program.

Following members attended the meeting:

1. Prof. D. K. Pal, Former HoD Community Medicine, GMC, Bhopal.....Chairperson
2. Prof. Rajnish Joshi, Professor of General Medicine, AIIMS, Bhopal.....Member
3. Prof. Amit Agrawal, Professor of Neurosurgery, AIIMS, Bhopal.....Member
4. Dr. Sunita Athawale, Addl. Professor of Anatomy, AIIMS, Bhopal.....Member
5. Dr. Ujjawal Khurana, Asst. Professor of Pathology, AIIMS, Bhopal.....Member
6. Dr. Ankur Joshi, Asst. Professor of CFM, AIIMS, Bhopal.....Member
7. Dr. Shubham Atal, Asst. Professor of Pharmacology, AIIMS, Bhopal.....Member
8. Ms. Kakoli Roy, Social Scientist.....Member
9. Mr. Trivesh Goswami, Law Officer, AIIMS-Bhopal,.....Member
10. Dr. Shashank Purwar, Addl Prof. of Microbiology, AIIMS, Bhopal...Member Secretary

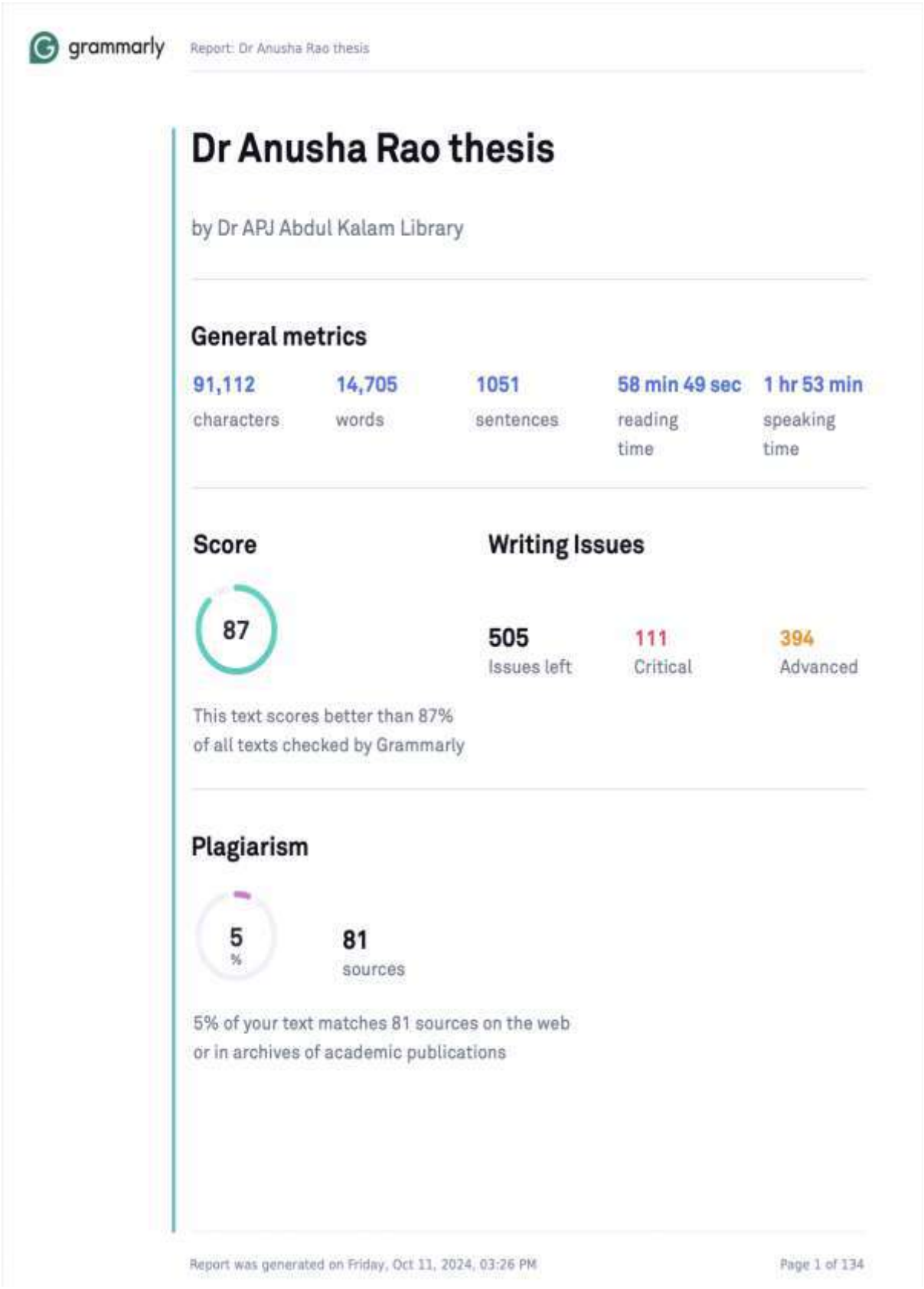
The decision of the committee is as follows:

The AIIMS, Bhopal IHEC-PGR approves your research protocol. All research related activities must begin only after the date of this approval. The validity of this approval is till two years from the date of issuance. Please submit a closure report / renewal request before expiration of the validity for this approval.

Shashank Purwar

Dr. Shashank Purwar
Member Secretary, AIIMS Bhopal IHEC-PGR
Additional Professor of Microbiology
AIIMS, Bhopal
Contact Number: 7773010099

PLAGIARISM CHECK



grammarly Report: Dr Anusha Rao thesis

Dr Anusha Rao thesis

by Dr APJ Abdul Kalam Library

General metrics

91,112	14,705	1051	58 min 49 sec	1 hr 53 min
characters	words	sentences	reading time	speaking time

Score

87

This text scores better than 87% of all texts checked by Grammarly

Writing Issues

505	111	394
Issues left	Critical	Advanced

Plagiarism

5 %

81 sources

5% of your text matches 81 sources on the web or in archives of academic publications

Report was generated on Friday, Oct 11, 2024, 03:26 PM

Page 1 of 134

ACKNOWLEDGEMENT

The journey through this thought-provoking, educative, informative novel work has enriched me with immense knowledge and experience. From the moment I chose the topic to the final stages of writing each step has been marked by periods of deep learning. As this work is successfully reaching its culmination I look back at the entire work and find it to be supported and blessed by many. It is my sacred duty to pay my debt of gratitude from the depth of my heart to everyone who has been a continuous source of inspiration during the entire course of the study.

I have no words to express my debt to my guide and mentor Dr Abhishek Goyal, whose brilliant foresight and practical approach coupled with exhaustive knowledge of the subject matter has been the guiding force behind all my efforts in giving shape to this project. He was always willing to give his precious time to resolve the many queries and doubts that arose during the course of the study. His expertise, patience, and unwavering support have sculpted this thesis and shaped my intellectual growth.

I would also like to express my heartiest gratitude to my co-supervisor Dr Alkesh Kumar Khurana, for giving his most invaluable time and efforts. It was due to his sheer knowledge and intelligent guidance that it was possible for this work to see the light of day.

I would also like to thank my co-supervisor Associate Professor Dr Ruchi Singh, for her cooperation, encouragement right from the very beginning and invaluable expertise which greatly contributed to the successful completion of the work. I am grateful for Dr Ruchi's patience and time.

I sincerely thank Dr Abhijit Pakhre for his constant support and help with the statistical work. His expertise is the bedrock upon which the analytical foundation of this thesis stands.

I want to extend my heartfelt thanks to my colleagues, Dr Prakhar and Dr Kirti, whose unwavering support in patient recruitment and invaluable guidance throughout my research were instrumental in helping me navigate through challenging times.

I would also like to thank my seniors and friends, Dr P Sai Tej, Dr Gaurav Sahu, Dr Amit Singh, Dr Bhupendra, Dr Asha, Dr Ayush, Dr Abhishek, Dr Hamza, Dr Ravi, Dr Rupal, Dr Akash, Dr Palash, Dr Alekhya and Dr Ankit for helping me out with valuable advice and for their help in patient recruitment.

This acknowledgement will remain incomplete if I fail to thank our staff Ms Deshanshi, Ms Neha and Ms Manju, Mr Parvesh, Mr Mukesh, Mr Amit, Mr Ankur, Mr Ranjeet, Mr Chetan for their valuable contributions and help with this study. It is no exaggeration to state that without their hard work and unconditional support, this work would not have been possible. For all that I know they have done for me, and for the many sacrifices they have made, I would like to thank my parents Mr. S. Madhusudana Rao and Mrs M.A. Visalakshmi and my husband Dr Venkatram. P for his constant encouragement in times of doubt and unconditional love.

A special thanks to my beloved twin daughters Ishanvi and Ishita for their love, patience, and smiles during this challenging process and for being my strength and motivation.

Finally, I thank the Almighty for giving me the courage to accomplish this work and I pray to Him to grant me the serenity to accept the things I cannot change, the courage to change the things I can and the wisdom to know the difference.

Dr S Anusha Rao

TABLE OF CONTENTS

S. No.	CONTENT	PAGE NUMBER
1	**Appendix I: List of Tables**	
2	**Appendix II: List of Figures**	
3	**Appendix III: List of Abbreviations**	
4	**Introduction**	1 - 6
5	**Review of Literature**	7 – 20
6	**Aims and Objectives**	21
7	**Materials and Methods**	22 – 31
8	**Results**	32 – 62
9	**Discussion**	63 – 70
10	**Summary**	71 – 72
11	**Strengths and Limitations**	73 – 74
12	**Conclusion**	75
13	**References**	76 – 87
14	**Annexures** • **Participant Information sheet** • **Patient Consent form** • **Data Collection form**	88 – 110
15	**Master Table**	111 - 113

APPENDIX-1. LIST OF TABLES

S.No.	Particulars	Page No.
1	Table 1: Parameters used for sample size calculation	24
2	Table 2: Baseline characteristics of patients as per the initial treatment arm	33
3	Table 3: Baseline HRV parameters of patients as per the initial treatment arm	41
4	Table 4: Baseline Ewing's battery of Autonomic function test parameters of patients as per the initial treatment arm	43
5	Table 5: Change in HRV parameters after 4 weeks of FPAP	46
6	Table 6: Change in HRV parameters after 4 weeks of APAP	47
7	Table 7: Change in Ewing's battery of Autonomic function test parameters after 4 weeks of FPAP	52
8	Table 8: Change in Ewing's battery of Autonomic function test parameters after 4 weeks of APAP	53
9	Table 9: Comparison of ESS, FSS and PSQI scores between FPAP and APAP	58
10	Table 10: Differences in PAP questionnaire after FPAP and APAP	61
11	Table 11: Comparison of Mean pressures (cm of H2O) between FPAP and APAP	62

APPENDIX-2. LIST OF FIGURES

S.No.	Particulars	Page No.
1	Figure 1: Flowchart depicting Study design	31
2	Figure 2: Mean Age (years) between FPAP and APAP as per the initial treatment arm	34
3	Figure 3: Number of males and females participated in the FPAP and APAP group as per the initial treatment arm	36
4	Figure 4: Mean BMI (kg/m^2) between FPAP and APAP as per the initial treatment arm	37
5	Figure 5: Mean NC, WC & HC (cm) between FPAP and APAP as per the initial treatment arm	38
6	Figure 6: Mean ESS between FPAP and APAP as per the initial treatment arm	39
7	Figure 7: Mean AHI between FPAP and APAP as per the initial treatment arm	40
8	Figure 8: Frequency domain parameters of HRV as per initial treatment arm	42
9	Figure 9: Time domain parameters of HRV as per initial treatment arm	42
10	Figure 10: B.P. and H.R. as per initial treatment arm	45
11	Figure 11: Ewings Battery of tests as per initial treatment arm	45
12	Figure 12: Change in frequency domain parameters after FPAP	49
13	Figure 13: Change in frequency domain parameters after APAP	49
14	Figure 14: Change in time domain parameters after FPAP	51
15	Figure 15: Change in time domain parameters after APAP	51
16	Figure 16: Change in B.P. and H.R. after FPAP	55
17	Figure 17: Changes in Ewing battery of tests with FPAP	55
18	Figure 18: Change in B.P. and H.R. after APAP	57
19	Figure 19: Changes in Ewing battery of tests with APAP	57
20	Figure 20: Comparison of ESS from baseline with FPAP and APAP	59

21	Figure 21: Comparison of FSS from baseline with FPAP and APAP	59
22	Figure 22: Comparison of PSQI from baseline with FPAP and APAP	60
23	Figure 23: Differences in PAP questionnaire after FPAP and APAP	61

APPENDIX-3. LIST OF ABBREVIATIONS

OSA	:	Obstructive Sleep Apnea
OSAS	:	Obstructive Sleep Apnea Syndrome
B.P	:	Blood Pressure
HTN	:	Hypertension
S.B.P	:	Systolic Blood Pressure
D.B.P	:	Diastolic Blood Pressure
H.R.	:	Heart Rate
BPM	:	Beats Per Minute
ANS	:	Autonomic Nervous System
BPV	:	BP Variability
PAP	:	Positive Airway Pressure
CPAP	:	Continuous Positive Airway Pressure
FP-CPAP	:	Fixed Pressure-Continuous Positive Airway Pressure
FPAP	:	Fixed-Pressure Positive Airway Pressure
APAP	:	Auto-Adjusting Positive Airway Pressure
BiPAP	:	Bilevel Positive Airway Pressure
PAP	:	Positive Airway Pressure
PSG	:	Polysomnography
AHI:		Apnea-Hypopnea Index
VLF	:	Very Low Frequency
LFnu	:	Low Frequency power
HFnu	:	High Frequency power
LF/HF ratio	:	Low frequency to high frequency ratio

NN	:	Normal to Normal interval
HRV	:	Heart Rate Variability
RDI	:	Respiratory Desaturation Index
BMI	:	Body Mass Index
SDANN	:	Standard Deviation of the Average NN intervals
SDNN	:	Standard Deviation of NN intervals
NREM	:	Non-Rapid Eye Movement
REM	:	Rapid Eye Movement
R-R interval	:	Time between two successive R-waves on Electrocardiogram
ECG	:	Electrocardiogram
SDNN	:	Standard Deviation of NN intervals
RMSSD	:	Root mean Square of Successive Differences
pNN50	:	Percentage of successive NN intervals that differ by more than 50ms
SDNN	:	Standard Deviation of NN intervals
SD1	:	Short term variability
SD2	:	Long term variability
QOL	:	Quality Of Life
RCT	:	Randomized Controlled Trials
MSNA	:	Muscle Sympathetic Nerve Activity
SDB	:	Sleep Disordered Breathing
RSA	:	Respiratory Sinus Arrhythmia
AASM	:	American Academy of Sleep Medicine
ESS	:	Epworth Sleepiness Scale
FSS	:	Fatigue Severity Scale
PSQI	:	Pittsburgh Sleep Quality Index

NC	:	Neck Circumference
WC	:	Waist Circumference
HC	:	Hip Circumference
AHI	:	Apnea-Hypopnea Index
BMI	:	Body Mass Index
CI	:	Confidence Interval
SD	:	Standard Deviation
SaO2	:	Arterial Oxygen Saturation

INTRODUCTION

Obstructive sleep apnea (OSA) refers to recurrent episodes of decline in or absence of airflow during sleep despite continuous efforts of the patient to breathe. Patients with OSA present with witnessed apnea, loud snoring, frequent awakening in sleep, excessive daytime sleepiness and periodic nocturnal hypoxemia[1,2]. According to a recent study, every third person in India between the age of 18-80 years has OSA[3]. The overall prevalence of OSA in the Indian population is estimated to be 13.7% (19.7% & 7.4% in males and females, respectively)[4]. OSA is associated with hypopnea and apnea due to repetitive episodes of partial or complete closure of upper airways, leading to changes in intrathoracic pressure, sleep fragmentation, surge in sympathetic activity and changes in heart rate regulation[5,6].

Even in healthy populations, sleep stages have a great impact on sympathetic and parasympathetic nervous system activity, thus associated with fluctuations in blood pressure and heart rate which are dependent on the sleep stage[7]. But sympathetic activity in OSA patients during sleep is dependent on apnea duration and severity, rather than sleep stage. Chemoreceptors and mechanoreceptors get stimulated by hypoxia, hypercapnia and mechanical stimulation due to obstructive apnea, resulting in an increase in sympathetic drive[8]. During an apnoeic event, due to an increase in vagal stimulation of the heart, there is bradycardia and more vulnerability of the heart to excitatory stimulus[9]. There is an increase in venous return after relieving obstruction and resumption of breathing, along with increased vascular tone, leading to an increase in cardiac output and blood pressure. Thus, normotensive OSA patients also will have a surge in blood pressure

at the end of the apnoeic event[8]. OSA patients have high sympathetic activity during sleep due to repetitive apneas, which are persistent during the daytime. Several mechanisms may contribute to the persistent high sympathetic activity, which includes dysfunction of chemoreflex and baroreflex[10], nocturnal endothelin release leading to vasoconstriction[11] and endothelial dysfunction[12]. The high sympathetic activity results in cardiovascular variability[10]. The abnormal cardiovascular variability in normotensive OSA patients may precede hypertension and cardiovascular disease. There is an increased chance of end-organ damage, as they are dependent on absolute blood pressure, in hypertensive patients with increased cardiovascular variability[13]. In OSA patients with already known cardiovascular disease, adverse outcomes are associated with abnormal heart rate variability[14,15].

Autonomic alterations may be detected by several methods. It includes both direct evaluation with microneurography, plasma catecholamines, urinary catecholamines, laser doppler flowmetry and indirectly by skin conductance, heart rate variability, blood pressure variability, near-infrared spectroscopy and by conventional Ewing's battery of tests, which includes heart rate response to active standing from the supine position, heart rate response to Valsalva manoeuvre, heart rate response to slow deep breathing, B.P. response to hand grip, B.P response to active standing from the supine position, B.P response to cold pressure[16,17]. Chronic sympathetic activation in OSA patients leads to vascular remodelling and resistant hypertension[18]. The threshold of cardiovascular adaptation may get reset by chronic overstimulation of ANS, resulting in abnormalities of autonomic functions which are assessed by Ewing's battery of tests.

Heart rate variability, one of the tests for functional evaluation of the autonomic nervous system, is an indicator of neurocardiac function generated by heart-brain interactions. HRV is calculated by assessing the cardiac cycle, from the fluctuations in heart rate. It reflects the relationship between the parasympathetic nervous system and the sympathetic nervous system and is a good predictor of future cardiovascular problems[19]. HRV is a measurement of changes in the time intervals between consecutive heartbeats. It can be described as long-term (24 hr), short-term (~5 min) and ultra-short term (<5 min) recording using time-domain, frequency-domain, and non-linear measurements.

The metrics of short-term time-domain indices include Root Mean Square of Successive RR interval differences (RMSSD), number of pairs of NN interval that is longer than 50 msec, percentage of numbers of pairs of NN that is longer than 50 (pNN50), HR Max-HR Min. Frequency domain indices include LF/HF, VLF, LF, and HF rhythms that operate within different frequency ranges: very low frequency (VLF) at 0.0033-0.04 Hz, low frequency (LF) at 0.04-0.15 Hz and high frequency component at HF 0.15-0.40 Hz. LF/HF ratio is considered a global index of the sympatho-vagal balance. Non-linear measurements include SD1-Pointcare plot standard deviation perpendicular to the line of identity, SD2-Pointcare plot standard deviation along the line of identity, SD1/SD2%.

Conventionally, the 24-hour period was used for HRV recording, but the reproducibility of the shorter sampling period of HRV has been recently demonstrated[20,21]. Longer recordings better represent processes with slower fluctuations like circadian rhythms and the cardiovascular system response to a wider range of environmental stimuli and workloads. Short-term HRV measurements are generated by two distinct but overlapping

processes. The first one being dynamic relationship between the sympathetic and parasympathetic branches of ANS and the second process includes the regulatory mechanisms that control H.R. via respiratory sinus arrhythmia (RSA), which refers to the respiration-driven changes of the heart via the parasympathetic system[22], the baroreceptor reflex (negative-feedback control of B.P), and rhythmic changes in vascular tone[23].

Cardiac autonomic modulations, as measured by HRV, are significantly altered in OSA. Patients with OSA exhibit increased low-frequency (LF) modulations, decreased high-frequency (HF) modulations, and increased LF/HF ratio during sleep[24–26]. LF reflects the cardiac response to sympathetic and parasympathetic impulses, whereas HF reflects only the cardiac response to parasympathetic impulses.

Diagnosis of OSA done by Level I polysomnography (PSG) and manual PAP titration is laborious and expensive thus, home-based sleep apnea testing and titration are prevalent. Pressure titration is done at 90/95th percentile pressure of APAP titration. However, studies showed that this strategy may not be sufficient if residual RDI <10 events/hr is the therapeutic target[27].

Continuous positive airway pressure (CPAP) is the gold standard treatment for OSA[28]. The CPAP machine splints open the airway by increasing luminal pressure and relieving the airway obstruction. When used properly and regularly, CPAP results in improved sleep patterns and quality of life due to decreased daytime somnolence.

Two types of CPAP devices are available. The fixed pressure CPAP (FPAP) and Auto-adjusting CPAP (APAP). Fixed pressure continuous positive airway pressure is the first

treatment for moderate to severe OSAS which forces a pre-fixed air pressure level on the upper airways[29,30]. FPAP not only improves OSAS-related symptoms such as snoring and excessive daytime sleepiness but also decreases mortality and morbidity related to cardiovascular complications[31]. Positive effects of CPAP therapy on cardiovascular and metabolic parameters are due to cessation of hypoxia and improvement in autonomic nervous system regulation [32,33]. FPAP treatment improves HRV by correcting the autonomic imbalance[34].

With recent technological developments, auto-titrating positive airway pressure (APAP) devices are added to PAP treatment as an alternative treatment modality, in which auto-set pressure level is given to the upper airways correspondingly to the obstruction severity, giving better compliance to the patient than FPAP.

Studies suggest that APAP is as effective as FPAP in terms of normalization of the apnea-hypopnea index (AHI) and improvement in sleepiness, quality of life, and neurocognitive function. Though using APAP has the advantage of significantly lower mean pressure applied during the night[35], which could theoretically improve patient comfort with the device, thereby enhancing adherence to therapy; however, no significant change in adherence was seen when compared to FPAP[36]. The pressure delivered by APAP is algorithm-based, which is proprietary owned by APAP manufacturers and often not disclosed. With automatic inadvertent increases in pressure, APAP can lead to the development of treatment-emergent central sleep apnea or periodic breathing in certain patients[37]. Few studies have shown that APAP is not as effective as FPAP in reducing sympathetic tone during sleep[38] or in improving cardiovascular risk factors in OSA

patients[39]. These findings might be due to microarousals caused by variations in therapeutic pressures during sleep and unintentional leakage caused by sudden increases in therapeutic pressure in response to respiratory events[40]. In a study, patients on APAP, who were not adherent and complained of persistent symptoms or side effects were switched to FPAP. After switching from APAP to FPAP, adherence and sleepiness of patients were improved[41].

Hence the present study is undertaken to compare both fixed CPAP and APAP therapies in the treatment of OSA and their efficacy in the improvement of cardiac autonomic activities in OSA patients.

REVIEW OF LITERATURE

OSA is one of the most common yet underdiagnosed sleep disorders in daily practice. In a study estimating the prevalence of OSA among the population aged 30-69 years, around 936 million had mild to severe obstructive sleep apnoea, among which 425 million population had moderate to severe obstructive sleep apnoea[42]. China has the highest number of OSA cases, followed by the USA, Brazil, and India. In a recent systematic review, around 104 million Indians of working age have OSA, out of which 47 million have moderate-to-severe OSA[43]. The prevalence of OSA in the elderly increases compared to the general population, with a prevalence of 90% in men and 78% in women[44]. OSA patients are at increased risk of cardiovascular complications due to high levels of sympathetic drive, even during wakefulness[45]. The extent of cardiovascular variability is linked to the severity of OSA, such that moderate to severe OSA patients are predominantly affected by dysfunctional cardiovascular variability[45]. In patients with severe OSA, there is a decrease in RR interval variability and B.P variability is augmented[10]. CPAP is the first-line therapy of OSA patients with proven efficacy and safety. PAP therapy provides pressurized air to keep the airways open, thus preventing airflow interruption during sleep[46]. Long-term PAP therapy improves cardiovascular function, reduces excessive daytime sleepiness, quality of life and reduces systemic complications of OSA[47,48]. Manual titration is required to estimate the therapeutic pressure requirement. CPAP delivers a continuous, fixed, air pressure throughout the respiratory cycle. APAP is another treatment option in OSA patients delivering variable airway pressure adjusting according to the AHI that is continuously assessed by the APAP device[49]. APAP is as effective as CPAP in terms of normalization of the apnea-

hypopnea index (AHI) and improvement in sleepiness, quality of life, and neurocognitive function, in compliance to therapy. However, APAP has the advantage of significantly lower mean pressure applied during the night compared to CPAP in a few studies[50]. However, recently APAP has been preferred over CPAP due to higher cost and limited resources associated with lab manual titration. Data comparing CPAP and APAP cardiac autonomic functions indicating cardiovascular health are limited.

Effect of PAP therapy on cardiac autonomic functions in OSA patients

Study comparing short-period sampling of HRV in the morning:

Pimporn Limphanudom MD et al[21] conducted a study from September 2004 to September 2006 in 10 newly diagnosed moderate to severe OSA patients. Out of 10 patients, 6 had severe OSA and 4 had moderate OSA. All the patients were men. They had given CPAP treatment for one, three and six months duration and have assessed ANS activities. There was wide variation in compliance with CPAP, which ranged from 2.27-5.15 hours in one month. Compliance at six months was 1.10-5.12 hours. To avoid circadian variation, the HRV parameters study was done between nine and twelve A.M. HRV analysis was done by 5-minute recording and LFnu, HFnu, LF/HF ratio and SDNN were measured. By the end of six months of treatment with CPAP, only SDNN during deep breathing improved in 7 out of 10 patients. Frequency domain parameters that include LFnu, HFnu and LF/HF ratio were not affected. Three patients were non-responders and showed a decrease in SDNN values out of which two had poor compliance to CPAP which was less than two hours per night.

Studies comparing HRV parameters between APAP night and CPAP night:

A prospective study was conducted by Levent Karasulu et al[51] comparing acute effects on HRV parameters in severe OSA patients overnight on CPAP and APAP. Forty newly diagnosed patients with OSA were enrolled for the study, and 5 patients were excluded due to CPAP intolerance and sub-optimal CPAP titration. Thus, 35 patients underwent a study with APAP mode after 1 week of full-night manual CPAP titration. The upper and lower limits of APAP device pressure were 4 and 15 cmH2O respectively. After one week of washout period, another PSG with CPAP was done and pressure was adjusted to optimal pressure according to the results of the titration night. Further, two patients refused CPAP treatment, and five patients were excluded because they lacked adequate segments in HRV analysis. Thus, the data of 28 patients was finally analysed. Among the 28 patients, 22 were males and 6 were females. The mean age and BMI of patients were 46±10 years and 29±4, respectively. Time domain parameters of HRV, RMSSD and SDANN and frequency domain parameters of HRV, VLF, LF, HF nuLF, nuHF and LF/HF were analysed during initial titration with CPAP, APAP therapy night and CPAP therapy night. RMSSD and SDANN were 55.71 ± 46.57, 46 ± 52.43, 46.67 ± 49.91 and 77.03 ± 43.83, 59.35 ± 43.85, 73.03 ± 47.83 respectively. Thus, there was no statistical difference in RMSSD and SDAAN values during the three study nights. Frequency domain parameters of three study nights were as follows: VLF was 3.93 ± 0.20, 3.84 ± 0.15, 3.86 ± 0.17, LF was 3.60 ± 0.19, 3.47 ± 0.20, 3.48 ± 0.19 HF was 3.03 ± 0.28, 2.93 ± 0.31, 3.01 ± 0.31, nuLF was 0.76 ± 0.11, 0.75 ± 0.13, 0.71 ± 0.14, nuHF was 0.23 ± 0.11, 0.24 ± 0.13, 0.27 ± 0.14 and LF/ HF ratio was 4.56 ± 3.23, 4.37 ± 3.24, 3.56 ± 2.07. Thus, nuLF, nuHF and LF/HF values improved statistically with CPAP therapy but not with APAP. HRV analysis of each stage of the sleep was done. Frequency domain

parameters of stage 2 of the three study nights were as follows VLF was 3.81 ± 0.44, 3.60 ± 0.40, 3.46 ± 0.46, LF was 3.63 ± 0.30, 3.51 ± 0.25, 3.30 ± 0.28, HF was 3.01 ± 0.35, 2.93 ± 0.36, 3.11 ± 0.32, nuLF was 0.75 ± 0.21, 0.76 ± 0.12, 0.60 ± 0.11, nuHF was 0.24 ± 0.21, 0.24 ± 0.12, 0.39 ± 0.11 and LF/HF was 5.97 ± 4.94, 5.15 ± 4.98, 1.75 ± 0.79. Thus LF, nuLF, nuHF and LF/HF values in stage 2 of the improved with CPAP and not with APAP. There were many limitations of the study, which included, analysis of only one APAP algorithm, the difference in respiratory rate and minute ventilation in HRV segments did not reach the statistical significance and there was no randomization in CPAP and APAP groups. Thus, the study showed that acute APAP treatment is inferior to CPAP treatment in improving autonomic dysfunction in OSA patients.

Studies assessing HRV parameters with acute CPAP treatment:

In a single-centre transversal retrospective study conducted by Kufoy E et al[52], patients with severe OSA totally corrected with CPAP were evaluated. After assessing inclusion and exclusion criteria, 39 patients were enrolled in the study, out of them 15 were females and 24 were males. The mean age and AHI were 50.67 years and 48.54 events/hr respectively. The mean BMI of the patients was 33.41 kg/m^2. Out of thirty-nine patients, twenty patients were obese with a BMI>30 kg/m^2 and six were morbidly obese with a BMI>35 kg/m^2. The study was to determine changes in Heart Rate Variability (HRV) in OSA patients after acute (single night) CPAP treatment. Patients underwent two sleep studies on consecutive nights, a basal study on the first night, and the second night with CPAP. Heart Rate Mean (HRM) and HRV were compared between the sleep stages during basal and CPAP studies. A 20-minute segment of data was analysed to calculate HRV. Heart rate mean, SDNN, apnea duration, minimal oxygen saturation, mean oxygen

saturation and variance of oxygen saturation were calculated. During the baseline sleep study, HRM was 73 bpm in wakefulness, which was higher than sleep, but it was similar in non-REM and REM stages of sleep, which were 64 bpm and 63 bpm respectively. Similarly, in CPAP studies, HRM was 73 bpm in wakefulness and 63 bpm and 61 bpm in non-REM and REM stages of sleep. In the CPAP study, the SDNN time domain variable of HRV was only significantly lower in the NREM stage (0.490 msec) compared to wake (0.0837 msec) or REM sleep (0.0610 msec). A multivariable analysis was also performed to determine whether there is any relationship between HRV and gender. HRM in wake was F=4.311, p=0.042, NREM was F=5.021, p=0.029 and REM was F=13.157, p=0.001. HRV in wake was F=6.124, p=0.016, NREM was F=3.426, p=0.069 and REM was F=3.509, p=0.066. No significant differences were seen in the HRM while comparing the basal study to the CPAP study($p>0.05$). HRV was only significantly lower in the NREM stage compared to wake or REM sleep in the CPAP study compared to the basal study. There was a significant difference between male and female groups during the wake in HRV and HRM. However, the changes were similar in the basal and in the CPAP nights, which suggests that gender does not influence the improvements seen in ANS activity from CPAP treatment.

Patruno V et al[38], have done a retrospective study by analysing full-night polysomnographic studies of 19 newly diagnosed patients with severe OSA. 7 obese subjects without OSA were taken as controls to test the effects of CPAP and APAP on autonomic regulation and cardiorespiratory coupling during sleep. After fixed-CPAP titration, all subjects were assigned to receive either a fixed-level CPAP or an auto-adjusting CPAP device with the same device but in auto mode for one-week duration.

Out of nineteen patients, nine received APAP and ten received CPAP. Mean age distribution in controls, APAP and CPAP groups were 48 ± 10, 45 ± 10 and 50 ± 12. Mean BMI and AHI in controls, APAP and CPAP groups were 36 ± 1, 37 ± 4, 36 ± 2 and 2 ± 2, 47 ± 15, 46 ± 15. PSG recordings were used to derive ECG and respiratory traces. Then, it is further divided into wake, N1, N2, N3 and REM stages. 5-8 segments lasting for 180 sec were analysed for each sleep stage. HRV and respiration were used to assess autonomic profile and coherence (K2) between respiration and HF oscillation during sleep. ECG and respiratory traces were derived from PSG recordings and then divided into Wake (W), N1, N2, N3 and REM stages. For each sleep stage, analysis of ECG and respiratory traces for a minimum of 5 segments (range 5–8) lasting 180 s was done. The analyses was done by two-way ANOVA and Bonferroni's post hoc test analysis. Mean RR in controls, APAP and CPAP groups in the wake were 924 ± 36, 1042 ± 34 and 905 ± 45, in the N2 stage were 906 ± 11, 1046 ± 14 and 928 ± 13, in the N3 stage were 906±18, 1094±14 and 934±14 and in REM were 925 ± 16, 997 ± 13 and 982 ± 14. LFnu in controls, APAP and CPAP groups in wake were 26 ± 6, 39 ± 6, 34 ± 4, in N2 were 28 ± 2, 53 ± 2, 33 ± 2, in N3 were 21± 3, 38 ± 2, 23 ± 2 and in REM were 43 ± 4, 53 ± 3 and 44 ± 3. HFnu in controls, APAP and CPAP groups in wake were 66 ± 7, 47 ± 7, 54 ± 5, in N2 were 58 ± 2, 46 ± 3 and 64 ± 2, in N3 were 68 ± 3, 51 ± 2, 70 ± 3 and in REM were 46 ± 3, 33 ± 3, 44 ± 3. Thus, in CPAP and control groups, LFnu and LF/HF decreased from N2 to N3 and increased during REM sleep while in the APAP group, sympathetic modulation was significantly higher compared to those of CPAP and control groups during all the stages of sleep. K2 values were lower in APAP compared to those in CPAP and control groups. APAP treatment was therefore characterized by a greater

sympathetic activation and associated with a lower cardio-respiratory coupling compared with CPAP. Limitations of the study were that there was no randomisation, and a single algorithm was used for testing.

To assess the impact of short-term (one night) and long-term CPAP therapy (2 years) on HRV during sleep and wakefulness, Palma JA et al[53] conducted a prospective study in patients with moderate to severe OSA, with a control group in the Caucasian population. 30 patients with OSA were studied out of which 16 patients with moderate OSA and 14 with severe OSA. A baseline study was conducted followed by a second PSG using CPAP pressure calculated from AHI, BMI and neck circumference. If AHI improved to ≤ 10 with the lowest oxygen value ≥ 85% CPAP therapy was considered successful and were included in the study. Patients were further given CPAP therapy for two years. Follow-up visits were done every six to nine months. Compliance data was obtained from the data from the built-in memory of the CPAP device at the end of two years. Only patients who used CPAP for ≥ 4 h/night on 70 % of nights were considered compliant and underwent the third PSG study. At two years of follow-up, patients were compared with each other and with 20 age and gender-matched controls. HRV analysis was done from ten-minute epochs in each sleep stage. Kruskal–Wallis test was used for comparisons among three or more groups and Bonferroni's post hoc test was used for multiple comparisons. A linear regression model was used to assess the effects of BMI and AHI on the spectral components of HRV. Simple linear model for estimating crude effect and multiple linear regression model for estimating the adjusted effect of age and BMI. During the baseline study, severe OSA patients exhibited higher LF power during NREM. Both moderate OSA and severe OSA patients exhibited higher LF modulations

during REM, lower HF modulations during NREM and REM, and a higher LF/HF ratio during NREM and REM. No differences were observed during wakefulness. In patients with moderate OSA with chronic CPAP use, the LF/HF ratio decreased during NREM and there was an increase in HF power, reduction in LF power and LF/HF ratio during REM. However, similar changes were not seen after acute CPAP therapy. In patients with severe OSA, both acute and chronic CPAP therapy decreased LF power and increased HF power during NREM and REM and decreased LF/HF ratio during REM. However, a decrease in LF/HF ratio was observed during NREM only after chronic CPAP use. No differences were observed during wakefulness. Thus, the study concluded that long-term CPAP treatment in OSA patients increased para-sympathetic modulation of the heart both in the NREM and REM phases of sleep and hence reduces the sympathovagal imbalance with the potential to decrease the risk of death in those patients.

Studies assessing Ewings battery of tests in OSA patients on CPAP treatment:

Quadri F et al[54] conducted a prospective study in overweight patients with severe OSA to evaluate the effects of CPAP on cardiovascular autonomic abnormalities and exercise performance. The patients enrolled were between 40 and 80 years and had a BMI ≥ 28Kg/m^2. The mean age and BMI of the patients were 58 ± 9.7 years and 33.3 ± 5.2 Kg/m^2, respectively. The mean AHI and oxyhaemoglobin saturation (SpO2) of the patients were 45.4 ± 14.9 events/ hour and 89.9 ± 3.5%, respectively. Patients underwent home-based cardiorespiratory monitoring during sleep to assess the severity of OSA and titration with CPAP was done to the pressure adequate to prevent upper airway collapse. Then, patients underwent a battery of tests to assess cardiovascular autonomic system function, which included deep breathing test, valsalva manoeuvre, head-up tilt test and

handgrip test and symptom-limited cardiopulmonary exercise test by cycle ergometer by incremental work protocol at 10-15 watts per minute. Then patients were given two months of treatment with CPAP and were asked to maintain their lifestyle and body weight during the study period. Cardiovascular autonomic nervous system activity was investigated by performing an Ewing battery of autonomic function tests and HRV and cardiopulmonary exercise tests were repeated at the end of two months in all the patients. With CPAP, there was increase of the high frequencies (HF) power component (28.9 ± 11.6) compared to the baseline (17.8 ± 11.5) with $p<0.05$, showing greater cardiac parasympathetic activity and a decrease of low frequencies (LF) power component (1.8 ± 1.4 msec2) compared to the baseline (5.4 ± 5.7 msec2) and thus the LF/HF ratio in the supine position with $p<0.05$, thus suggesting reduction in cardiac sympathetic activity. Heart rate response to the Deep Breath test at baseline and with CPAP therapy was 11.9 ± 8.6 and 15.3 ±10.6 Δbeat/max-min; $p<0.01$) and systemic blood pressure response to the Handgrip test was 25.8 ±13.4 vs 46.5 ±16.7 ΔmmHg; $p<0.01$). Thus both increased, suggesting a decrease in sympathetic activity. The limitation of the study was a small number of the study population. After CPAP, an increase of the high frequency (HF) power component and a decrease of both the low frequency (LF) power component and the ratio between low and high frequencies (LF/HF) in the supine position were observed. Heart rate response to the Deep Breath test and systemic blood pressure response to the Handgrip test were increased. Thus, CPAP therapy in overweight OSA patients was associated with reduced sympathetic activity. Following the CPAP treatment, there was greater exercise capacity that was associated with reduced sympathetic nerve activity. The benefit might occur through better balance of the autonomic nervous system activity

by improved muscle energy metabolism, restoration of the aerobic enzymes function and reduction in mitochondrial oxidative.

Veale D et al. conducted a prospective study[55] to assess ANS function, pre and post-treatment with nasal CPAP for one year in six patients with moderately severe and severe OSA. The mean age and BMI of the patients were 52 ± 5 years and 32.2 Kg/m^2 respectively. PSG was done at the diagnosis of OSA and with nasal CPAP. All the patients were symptomatic due to OSA before treatment, but none complained of any autonomic-related symptoms before or after nasal CPAP. Tests consisted of heart rate responses to the valsalva manoeuvre, deep breathing, and change of posture from lying to standing, systolic blood pressure (S.B.P) response to standing and diastolic blood pressure (D.B.P) response to hand grip. Each abnormal test was scored +1.0 and each marginal test (90–95% confidence interval for normal) was scored +0.5. A total score was calculated for the five tests performed in both the evening and morning, with a maximum score of 10 per patient. Out of six patients, five used nasal CPAP regularly with a mean usage of 7.1 ± 2.4 hours/night. Thus, the final analysis was done on five patients. Quantitative variables were compared using a Wilcoxon signed rank test and a Chi-squared analysis for comparison of qualitative variables. Yates' correction was done. All the patients showed normalization in the ANS test score after one year of CPAP treatment. Mean pre-nasal CPAP and post-nasal CPAP ANS test scores were 2 (1-4.5) and 0.2 (0-0.5) with total scores of 10.5 out of 45 and 1.0 out of 45 respectively. 45 was the possible maximum ANS test score for the five patients. There was an improvement in mean SaO2 during sleep post-CPAP treatment. One patient was not compliant with

CPAP, his post-CPAP ANS test score (1.5) worsened compared to pre-CPAP (1.0). Thus concluded that impaired autonomic response in OSA patients improves with nasal CPAP.

Studies assessing autonomic function in OSA patients by other methods:

A study was conducted by K. Narkiewicz et al[45] measuring blood pressure, heart rate, and MSNA (Muscle Sympathetic Nerve Activity) in 11 normotensive patients with OSA who were treated with CPAP. The measurements were obtained at baseline and with CPAP therapy after 1 month, 6 months, and 1 year. These measurements were compared with 9 otherwise healthy OSA patients who did not receive CPAP therapy for 1 year. In both untreated and treated patients, blood pressure and heart rate did not change over time. In the untreated group, during repeated measurements, MSNA was the same. By contrast, MSNA decreased significantly over time in patients treated with CPAP. There was no significant decrease in MNSA after 1 month of treatment with CPAP but the decrease was evident after both 6 months and 1 year of CPAP treatment (P=0.02 for both).

In a recent study, Treptow E et al conducted a prospective, double-blind, randomized controlled trial comparing the sympathetic activity in treatment-naive OSA patients after 4-week therapy of APAP and FPAP. Then, during a one-week titration phase, an auto CPAP device was used over eight nights at home to obtain optimal fixed CPAP pressure. Muscle sympathetic nerve activity (MSNA), urinal catecholamines, 24-hour B.P, calf blood flow, and HRV were measured at baseline and after FPAP and APAP. After assessing inclusion and exclusion criteria, patients underwent full night polysomnography, and those with AHI >20/hour and daytime sleepiness (Epworth Sleepiness Scale >10) were included in the study. Analysis was done by Student's t-test and linear mixed model. They found a significantly larger reduction of sympathetic tone

in the FPAP group, as evidenced by a decrease in MSNA bursts/min and urine epinephrine and norepinephrine levels. However, improvement in B.P was similar between the two arms. The use of home Auto CPAP titration for determining the optimal pressure for FPAP was one of the major limitations of the study. Overall, the study concluded that a higher reduction in sympathetic tone was achieved by FPAP as compared to APAP.[56]

Studies comparing office B.P. in OSA patients on APAP Vs CPAP :

Patruno et al[57] compared the efficacy of FPAP and APAP treatments in reducing cardiovascular risk in thirty-one patients with OSA. They included OSA patients, diagnosed after Level 1 PSG with AHI>20/hr and were free from other systemic diseases except hypertension. They underwent CPAP titration followed by randomisation into APAP and FPAP groups. They took three B.P readings and recorded the average of them. Office B.P. was recorded at baseline and after 3 months of treatment with each group. OSA indices were reduced in both groups following treatment. They observed a significant reduction in S.B.P (from 144 ± 10 to 132 ± 8 mm Hg) and D.B.P (from 88 ± 4 to 79 ± 6 mm Hg) in the FPAP group but not in the APAP group (S.B.P, from 142 ± 12 to 136 ± 6 mm Hg; D.B.P, from 87.5 ± 4 to 86 ± 4 mm Hg). FPAP reduced B.P. to a greater extent as compared to APAP. They concluded that FPAP and APAP, despite significant effects on OSA indexes and symptoms, do not improve cardiovascular risk factors. This study was limited by its small sample size and the measurement of only office B.P.

In 2016, Pepin et al[58] did a double-blind, randomised controlled trial comparing the efficacy of FPAP with APAP in reducing B.P. 322 patients between ages 18 and 80 years underwent Level I and III PSG, and those diagnosed with severe OSA were included in

the study after assessing inclusion and exclusion criteria. An auto CPAP device was used for eight nights at home to titrate the optimal pressure for FPAP. Patients were randomised to either the FPAP or APAP group for 4 months. Both office B.P and 24-hour B.P were measured. Change in clinical B.P. was taken as primary outcome whereas secondary endpoints included change in 24-hr B.P. measurements and pulse wave velocity. Office systolic blood pressure decreased by 2.2 mm Hg (95% CI -5.8 to 1.4) and 0.4 mm Hg (-4.3 to 3.4) in the FP-CPAP and Auto-CPAP groups, respectively. Thus, there was no significant reduction in office B.P as compared to baseline at the end of four months in both arms. However, 24-hour B.P. measurement showed statistical improvement. The major limitations of the study were the lack of in-laboratory CPAP titration and poor patient compliance. The percentage of patients with OSA using CPAP more than 4 hr/night was 64.6% and 66.5% in the FPAP and APAP arms. This is below the standard definition, which defines adequate adherence as CPAP usage for >4hr/night for more than 70% of days.

Studies comparing APAP vs FPAP effect on adherence, tolerance, symptoms, and patient's preference:

Alves et al[60] did a prospective study in ninety-three patients where patients were switched from APAP to FPAP. Patients with OSA using APAP with satisfactory compliance and adherence, and residual AHI of < 5/hour, with no relevant air leaks, were switched to FPAP. FPAP pressures were decided from the 90th or 95th percentile of APAP pressure, which was an effective alternative strategy to PSG titration. They found that both APAP and FPAP were effective in correcting obstructive events and improving daytime sleepiness. Adherence and tolerance between the two therapies were also similar and also cost-saving.

A blinded crossover RCT was done by Vennelle M et al[61] to assess OSA treatment with FPAP vs APAP. Two hundred CPAP naive OSA patients with daytime sleepiness were included and given FPAP and APAP for six weeks each. At the end of each six weeks following assessment was performed: objective sleepiness by modified Osler using 2 wakefulness trials, vigilance using psychomotor vigilance test and quality of life by short Form 36. Seventy-two patients preferred FPAP, and 69 preferred APAP therapy, thus did not show any difference in patient preference for either PAP therapy. There was a marginal benefit of APAP over FPAP in OSA in terms of subjective sleepiness. The ESS score was found to be lower in APAP as compared to FPAP (p=0.031), but its clinical significance remains to be determined since the objective sleepiness parameters measured by two 40 min Osler tests at 10:00 and 12:00 did not show any significant difference between FPAP and APAP.

Need for the present study:

There have been various studies to date comparing apnea-hypopnea index (AHI), improvement in sleepiness and quality of life in OSA patients using FPAP and APAP with varying results. However, there is a lacuna of literature comparing FPAP and APAP in terms of cardiac autonomic functions that signify cardiovascular risk in OSA patients. Therefore, studies comparing the effects of FPAP and APAP on various autonomic functions are required to determine the effectiveness of these therapies for cardiovascular risk reduction in OSA patients. Hence, the current study was carried out to compare the day-time effects of FPAP and APAP on frequency and time domain parameters of HRV and Ewing's battery of autonomic function tests, which are non-invasive methods of evaluation of autonomic activity in patients with moderate to severe OSA.

AIM AND OBJECTIVES

AIM:

- To compare the efficacy of FPAP and APAP on cardiac autonomic activities in moderate to severe OSA patients.

Primary Objective :

- To measure and compare the frequency domain parameters of Heart Rate Variability (LF/HF ratio, LF, HF) with reference to FPAP and APAP in moderate to severe OSA patients.

Secondary Objective:

1. To measure and compare time domain parameters (RMSSD, PNN50) of HRV with reference to FPAP and APAP in moderate to severe OSA patients.
2. To measure and compare the autonomic function test (Ewing's battery of tests) with reference to FPAP and APAP in moderate to severe OSA patients.

MATERIALS AND METHODS

Study setting:

- The study was carried out in the Department of Pulmonary Medicine and the Department of Physiology at AIIMS Bhopal.

Study population:

- Adult patients (age more than 18 years) diagnosed with moderate-severe obstructive sleep apnea by level I polysomnography in the Department of Pulmonary Medicine.

Study Duration:

- The duration of the study was 18 months.

Study Design Overview:

- The study was a prospective, randomised, cross-over study.

Conflict of interest: Nothing to disclose.

Ethical Clearance: Ethical clearance was taken from IHEC, AIIMS, Bhopal with Ref no IHEC-PGR/2022DM-MCh/Jan/07.

Inclusion criteria:

Treatment naive and recently diagnosed patients of age eighteen and above with moderate-severe OSA who achieved successful titration with PAP were included in this study.

Exclusion criteria:

- Pregnancy

- History of diabetes mellitus,
- Coronary artery disease, arrhythmias, cardiac failure
- Central Sleep Apnea (defined when central apnea or hypopnea constitutes 50% or more of the respiratory events and the central apnea index is 5/hr)[62]
- Psychiatric, and neurologic disorders preventing them from being compliant to treatment
- Patients with craniofacial abnormalities which can hamper the usage of CPAP mask.
- Patients with prior use or using CPAP

Statistical Analysis and Sample Size:

Analysis Plan:

The analysis of the cross-over trial was done from the perspective of pre-test to check the assumption of optimum carry-over period will be checked through summing of the values measured in two different periods was calculated for each participant and compared across the two sequence groups by paired test (either paired t-test or paired ANOVA or non-parametric equivalent).

The primary effect size of interest across different groups during a specified period was calculated by independent t-test / ANOVA or non-parametric equivalent. The effect measures across the period were checked to ascertain any specific difference (which may influence the effect measured) or statistical insignificance.

Sample Size:

In a previous study, a reduction of the LF/HF ratio from 5.4 ± 5.7 to 1.8 ± 1.4 was seen after two months of CPAP treatment. As our primary objective was to compare the

change in sympathovagal balance using LF/HF ratio from % minutes of HRV and other autonomic parameters, we used a t-test to detect effects in pre and post-interventions (time) within the group.

The following assumptions were used : t tests – Means: Differences between two dependent means (matched pairs)

Analysis: A priori: Compute required sample size

Table 1: Parameters used for sample size calculation

INPUT	Effect size f	0.6997220
	α error prob	0.05
	Power (1-β error prob)	0.95
OUTPUT	Non-centrality parameter λ	3.7681183
	Critical t	2.0484071
	df	28
	Total sample size	29
	Actual power	0.9531341

Thus, a total of 29 subjects were needed. Anticipating a non-response rate of around 10%, we planned to enrol 32 participants and finally enrolled 36 patients in the study.

Study Protocol:

Sleep Study:

Titration: Patients underwent Level I PSG { Philips Alice 6 (Philips Respironics; USA)} in the department of pulmonary medicine, AIIMS Bhopal.

Those with AHI≥15 underwent a split night study (Level I PSG) with manual CPAP titration polysomnography to determine optimal pressure. Electroencephalography, chin electromyography, leg electromyography, electrooculography, SpO2, chest and abdominal movements with zRIP belts, and body sensors were used in all patients. The American Academy of Sleep Medicine (AASM) criteria for scoring 2012 was used. Apnea is defined as the cessation of airflow ≥ 90% through the nose ≥ 10 sec, and hypopnea is defined as the reduction in airflow ≥ 30% associated with a decrease in the pulse oximetry reading (desaturation) ≥ 3% and/or arousal[63]. OSA is defined as an AHI ≥ 5. The severity of OSA will be described by the number of apneas and hypopneas per hour of sleep (AHI). OSA will be categorised into two categories based on AHI as follows: mild (AHI 5–14.9) and moderate-severe (AHI ≥ 15)[64].

Patients were titrated with CPAP if patient had AHI ≥ 15. For scoring rules of CPAP titration, the AASM Manual for the sleep and associated events was followed[65].

Randomisation: Thirty-six consecutive patients meeting the eligibility criteria were randomized by block randomization technique using serially numbered opaque sealed envelopes. Random number sequences were generated using a web-based random number generator and assigned by random table allocation into either APAP mode or FP-CPAP mode (ResMed auto-set CPAP machine) as the initial treatment. After randomization, all patients underwent baseline HRV and Ewing's battery of autonomic function tests. Patients were educated about CPAP machines and mask usage. Patients remained in the assigned treatment arm for four weeks, followed by a washout period of two weeks, and were then crossed over to the second arm of treatment for a further four

weeks. After the initial four weeks, the patient's PAP machine was analysed for usage, and he/she underwent HRV and Ewing's battery of autonomic function testing. Then the patient was switched over to other PAP therapy for four weeks patients, the PAP machine was again analysed for usage and he/she underwent final HRV and Ewing's battery of autonomic function testing after a washout period of 2 weeks. Along with HRV and Ewing's battery of autonomic function tests, the Epworth Sleepiness Scale (ESS) was used to measure daytime sleepiness, the Fatigue Severity Scale (FSS) assessed the impact of fatigue on patients' daily life and the Pittsburgh Sleep Quality Index (PSQI), evaluated sleep quality over one month, were also assessed at baseline and after each arm. The PAP questionnaire, which evaluates patients' experience, adherence and satisfaction with PAP therapy, was also evaluated after both FPAP and APAP. The mean FPAP pressure, measured during CPAP titration, was compared with the mean pressure delivered by APAP to analyze the average pressure delivered to the patients during the study.

Patients were advised to use a mask (nasal or full face) based on manual titration, and the same mask was used during both arms, to nullify the effect of different types of mask on treatment of OSA. During manual titration, those who could not be titrated optimally with CPAP titration (according to AASM titration) were advised BiPAP after titration, in the FPAP arm. Both fixed pressure-CPAP and auto-CPAP machines were provided free of cost to all patients during the study period. The patients and outcome assessment technicians were blinded to the arms to which the patients were allocated.

Patients were followed up weekly and could obtain advice from the sleep technologist by telephone at any time for any issue regarding the PAP device. Arrangements for an early

clinical review if needed were also made. The medical appointments were scheduled for all patients at the end of the 4th week (4 weeks after initial treatment arm), 6th week (after 2 weeks of washout period) and 10th week (4 weeks after second arm of treatment) after starting the PAP therapy for protocol-based assessments of the following: HRV, Ewing's battery of autonomic function testing, adherence to CPAP and antihypertensive treatment, changes in treatments, measurement of anthropometric variables, and re-evaluation of the exclusion criteria.

According to AASM, adherence was considered adequate if the mean PAP use was atleast 4 hours per night on 70% of nights and the average hours of PAP usage was > 4 hours daily[48].

Autonomic Functions :

The patients were evaluated for ANS activities between 9 and 12 AM to avoid circadian variation. During the study, subjects were given instructions and were evaluated for autonomic functions after fulfilling their prerequisite instructions. Before recording, patients were instructed to abstain from any type of exercise, eating and drinking anything and having caffeine 2 hrs before the scheduled time for the test. The patients were rested between each test for the heart rate to return to baseline.

HRV Measurement:

This is a reliable and non-invasive test used to explore the nature of sympathetic-parasympathetic interactions. HRV recording and assessment was done on the power lab (AD Instruments Pvt Ltd, Castle Hill Australia). ECG was sampled at 1000 Hz for 5 minutes with the Power Lab acquisition system.

HRV recording (short term for 5 minutes) was used for analysing the frequency domain (Total, LF, HF, LF: HF) and time domain parameters (RMSSD, pNN50).

Frequency Domain Parameters:

The measurement of LF and HF power components is usually made in absolute values of power (milliseconds squared). LF and HF, measured in normalized units[66], represent the relative value of each power component in proportion to the total power minus the VLF component. LF:HF is the ratio of LF to HF power.

Time Domain Parameters:

As we recorded short-term HRV of 5 minutes, RMSSD and PNN50 of time domain parameters were compared at various points of time.

RMSSD (Root Mean Square of Successive Differences between normal heartbeats) is obtained by first calculating each successive time difference between heartbeats in msec and then, each of the values is squared and the result is averaged followed by the square root of the total is obtained.

pNN50 is the percentage of adjacent NN intervals that differ from each other by more than 50 msec.

The recording was done once the patient became stable in a quiet room with a comfortable temperature.

Ewing's battery of Autonomic function tests:

Tests were conducted with an ECG machine(BPL) and sphygmomanometer with the patient lying on the tilt table, in the following order:

A) Tests of Parasympathetic Function

i. Heart rate response to active standing from the supine posture (30:15 ratio):

Patients were encouraged to lie comfortably on the tilt table and were strapped onto the tilt table. The tilt table was inclined to 60° on the inclinometer and ECG was recorded for 1 minute. R-R intervals of beats 15 and 30 after tilting were recorded and the 30:15 ratio was calculated.

ii. Heart rate response to the Valsalva manoeuvre:

Valsalva manoeuvre (Valsalva-Weber manoeuvre) evaluates the function of the baroreceptors. Patients were instructed to blow into the mouthpiece connected to the manometer so that the column was maintained at 40mm Hg for 15 seconds. ECG was recorded for 1 min for measurement of the Valsalva ratio. The R- R intervals of the ECG were examined and the Valsalva ratio is the ratio of the longest R-R interval during release to the shortest R-R interval during strain.

iii. Heart rate response to slow deep breathing (E: I):

This test evaluates the changes in heart rate with deep breathing that are mediated by the vagal nerve. Patients were instructed to breathe deeply at a rate of 6 breaths/minute with 5 seconds of inhalation and exhalation each in the supine position. ECG was recorded for a whole minute. The ratio of the mean of the maximum R-R intervals during deep

expiration to the mean of the minimum R-R intervals during deep inspiration was calculated.

B) Tests of Sympathetic Function

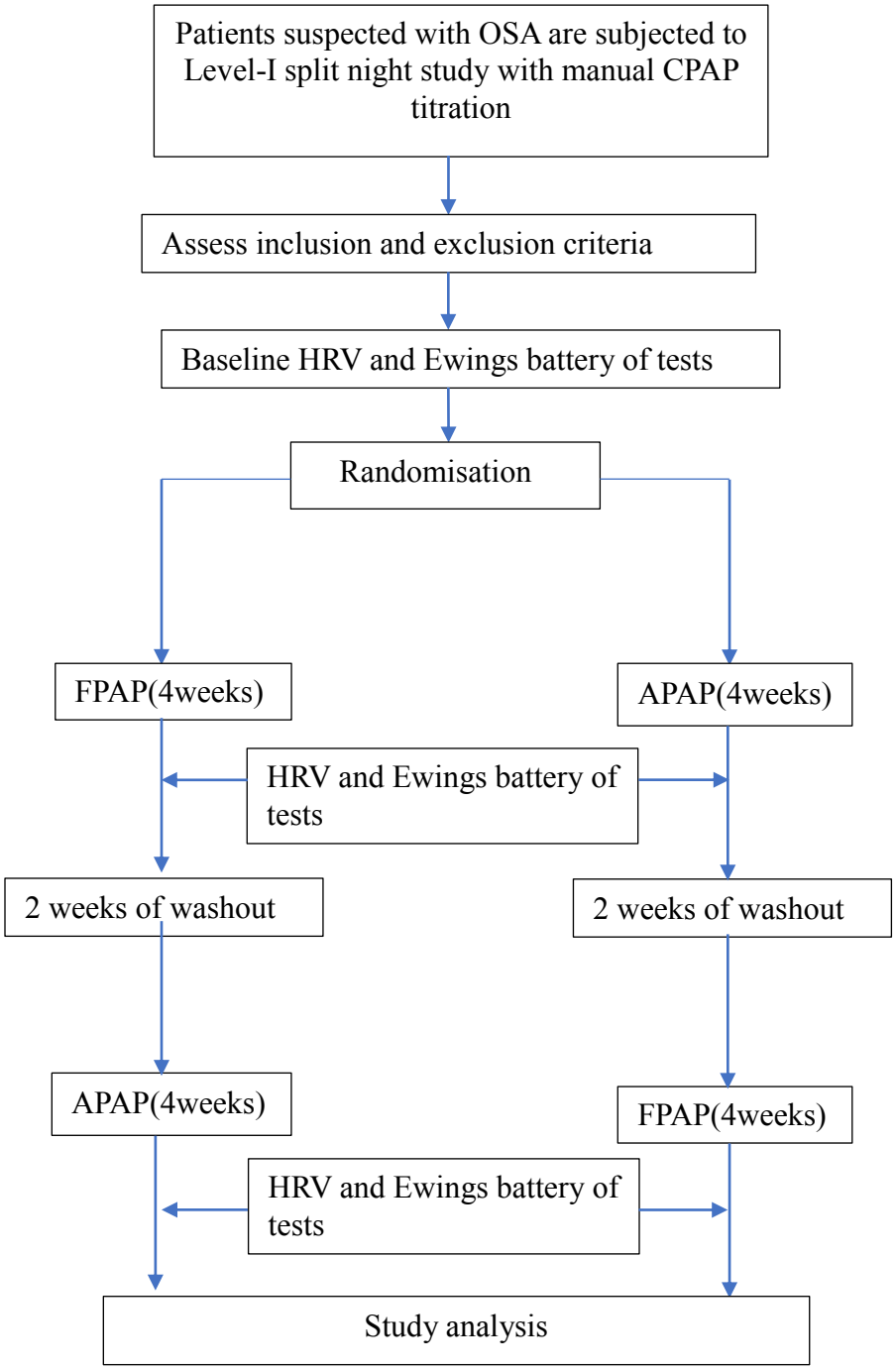
i. Blood pressure response to sustained handgrip :

This test is based on the principle of a rise in blood pressure as a result of the acceleration of heart rate without an increase in peripheral vascular resistance. This isometric exercise was performed using a handgrip dynamometer. The subject was in a sitting position while performing the test and was asked to compress the handgrip dynamometer for four minutes, at around 1/3rd of the maximum force the patient could generate. Blood pressure was measured on the non-exercising hand at a one-minute interval for four minutes. Handgrip response was the change in D.B.P recorded.

ii. Blood pressure response to active standing from the supine posture :

Patients were encouraged to lie comfortably on the tilt table and were strapped onto the tilt table. The tilt table was inclined to 60° on the inclinometer and B.P. was recorded at regular intervals for four minutes to observe the change in S.B.P. Postural Response was the difference in S.B.P calculated.

Figure 1: Flowchart depicting study design


Patients suspected with OSA are subjected to Level-I split night study with manual CPAP titration
Assess inclusion and exclusion criteria
Baseline HRV and Ewings battery of tests
Randomisation
FPAP(4weeks)
APAP(4weeks)
HRV and Ewings battery of tests
2 weeks of washout
2 weeks of washout
APAP(4weeks)
FPAP(4weeks)
HRV and Ewings battery of tests
Study analysis

RESULTS

One hundred and fifty patients who underwent overnight Polysomnography and manual titration were screened for eligibility at the Sleep lab at AIIMS Bhopal from September 2022 to March 2024. 36 patients fulfilling the inclusion and exclusion criteria were enrolled. All of them underwent baseline HRV and Ewing's battery of autonomic function tests. They were randomised to receive either APAP or FPAP as the first treatment modality with 18 patients being enrolled in each arm. 4 patients dropped out during the first arm of treatment and all the patients were from the FPAP arm. Thus, among the remaining 32 patients, 14 received FPAP and 18 received APAP in the first arm. Two patients in the FPAP arm did not come for follow-up, so they were excluded from the study. Finally, 12 patients from the FPAP arm and 18 APAP arm were included for final analysis. They underwent repeat HRV and Ewing's battery of autonomic function tests after one month of the first arm and were then switched to the other arm for another one month. A washout period of two weeks was given between the two arms. No dropouts were present in the second arm of treatment and HRV and Ewing's battery of autonomic function test was again repeated after the final arm. 30 patients were finally analyzed, among them, 5 patients could not be titrated with CPAP during the manual titration study and achieved optimal or adequate titration only on Bilevel PAP. Hence, they were given Bilevel PAP in the FPAP arm. Along with HRV and Ewing's battery of autonomic function test, ESS, FSS, and PSQI were also evaluated at baseline and after each arm. The PAP questionnaire was also evaluated after both FPAP and APAP. The mean FPAP and APAP pressures were analyzed and compared by the end of the study.

BASELINE CHARACTERISTICS

Table 2: Baseline characteristics of patients as per the initial treatment arm

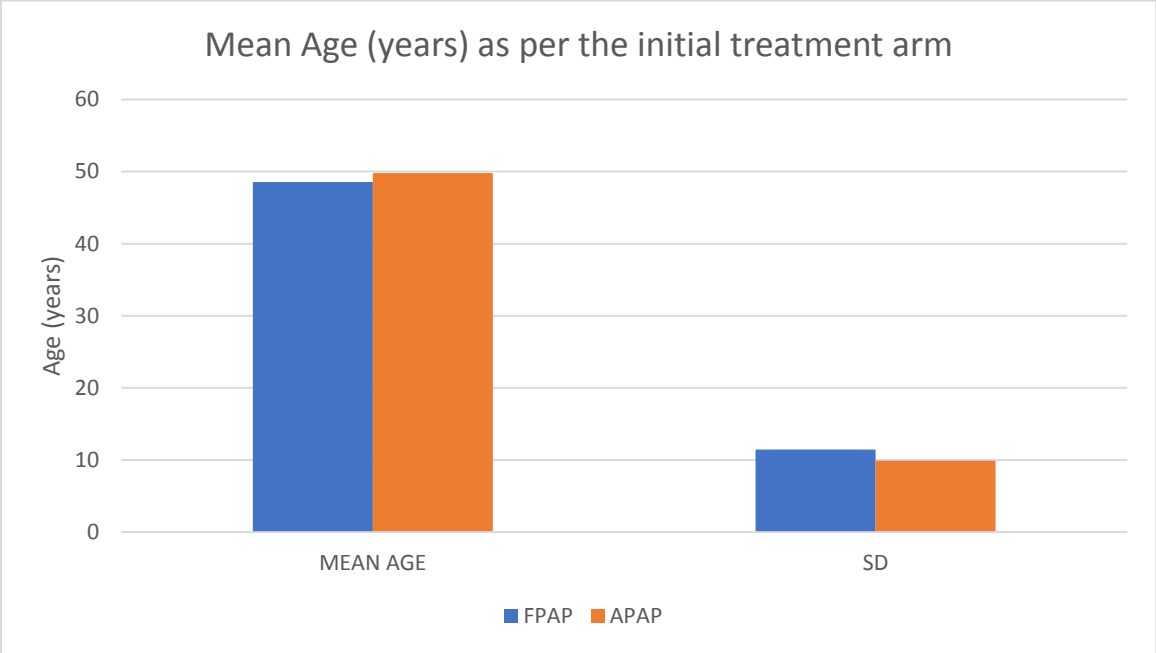
Baseline parameter	Initial treatment arm	N	Mean	Std.Deviation (SD)	p value
Age (years)	FPAP	16	48.56	11.46	0.635
	APAP	16	49.78	9.91	
BMI (Kg/m^2)	FPAP	16	30.29	4.44	0.591
	APAP	16	29.39	2.61	
NC (cm)	FPAP	16	38.39	4.19	0.824
	APAP	16	39.00	3.31	
WC (cm)	FPAP	16	104.50	10.04	0.419
	APAP	16	101.61	6.7	
HP (cm)	FPAP	16	103.72	7.34	0.646
	APAP	16	104.33	6.32	
ESS	FPAP	16	13.00	5.46	0.849
	APAP	16	12.17	6.06	
AHI (events/hr)	FPAP	16	66.74	31.35	0.975
	APAP	16	66.42	34.81	

BMI: Body Mass Index, NC: Neck circumference, WC: Waist circumference, HC: Hip circumference, ESS: Epworth Sleepiness Scale, AHI: Apnea-Hypopnea Index

AGE DISTRIBUTION:

The mean age of the 36 patients enrolled in the study was 49.17± 10.58 years. In the initial treatment arm, the mean age of patients allocated to the FPAP group (n=16) was 48.56 years and the APAP group (n=16) was 49.78 years (p= 0.635).

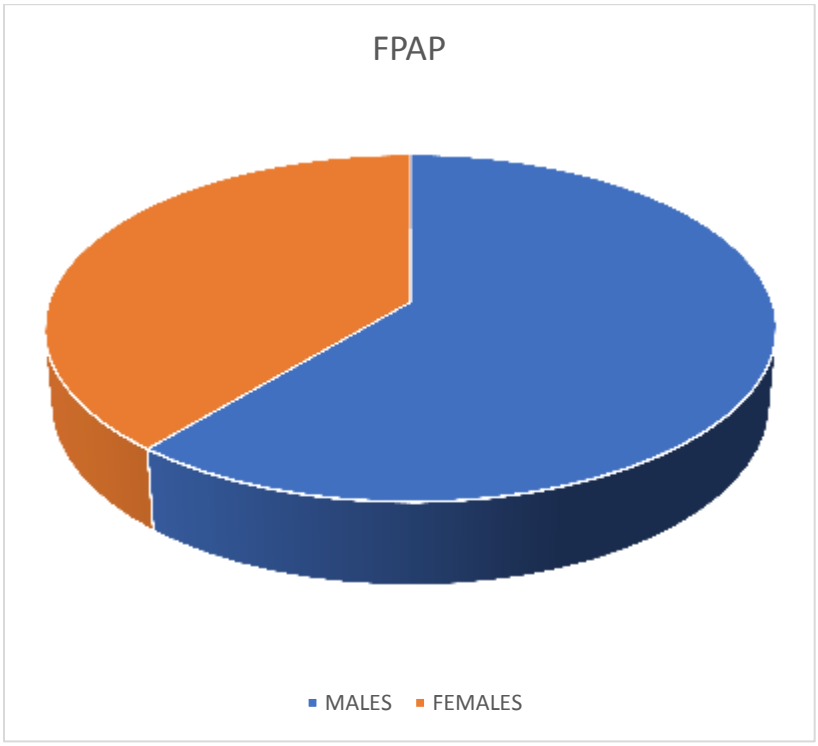
Figure 2: Mean Age (years) between FPAP and APAP as per the initial treatment arm

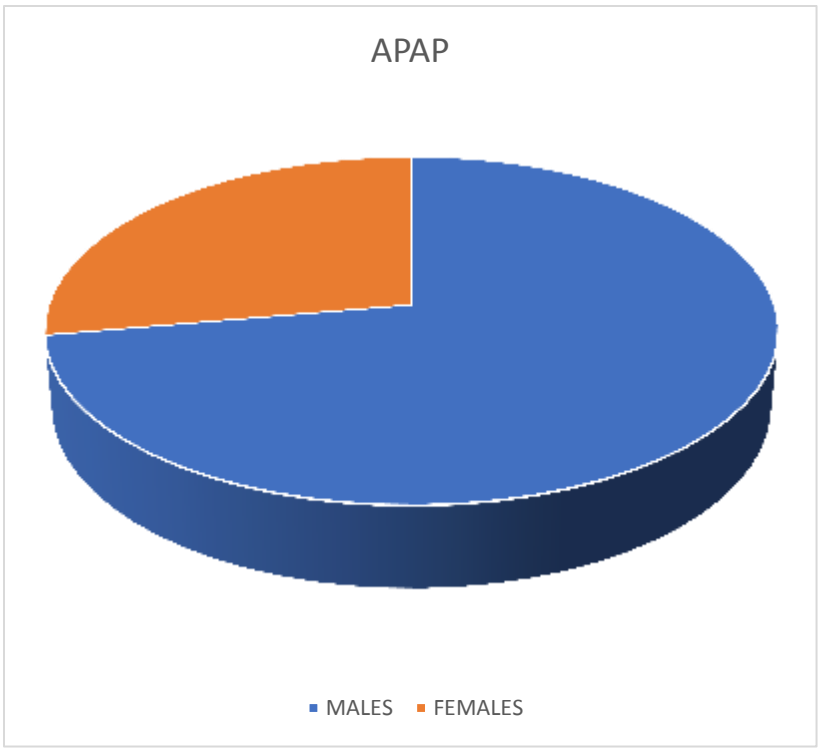


GENDER:

Among the 36 patients, 12 (33.3%) were females and 24 (66.7%) were males. Out of 18 who received FPAP as the first modality of treatment, 11 (61.1%) were male and 7 (38.9%) were female. Among the patients receiving APAP as the first modality, 13 (72.2%) were male and 5 (27.8%) were female. The difference between the two groups was not statistically different (p=0.48).

Figure 3: Number of Males and Females who participated in the FPAP and APAP group as per the initial treatment arm

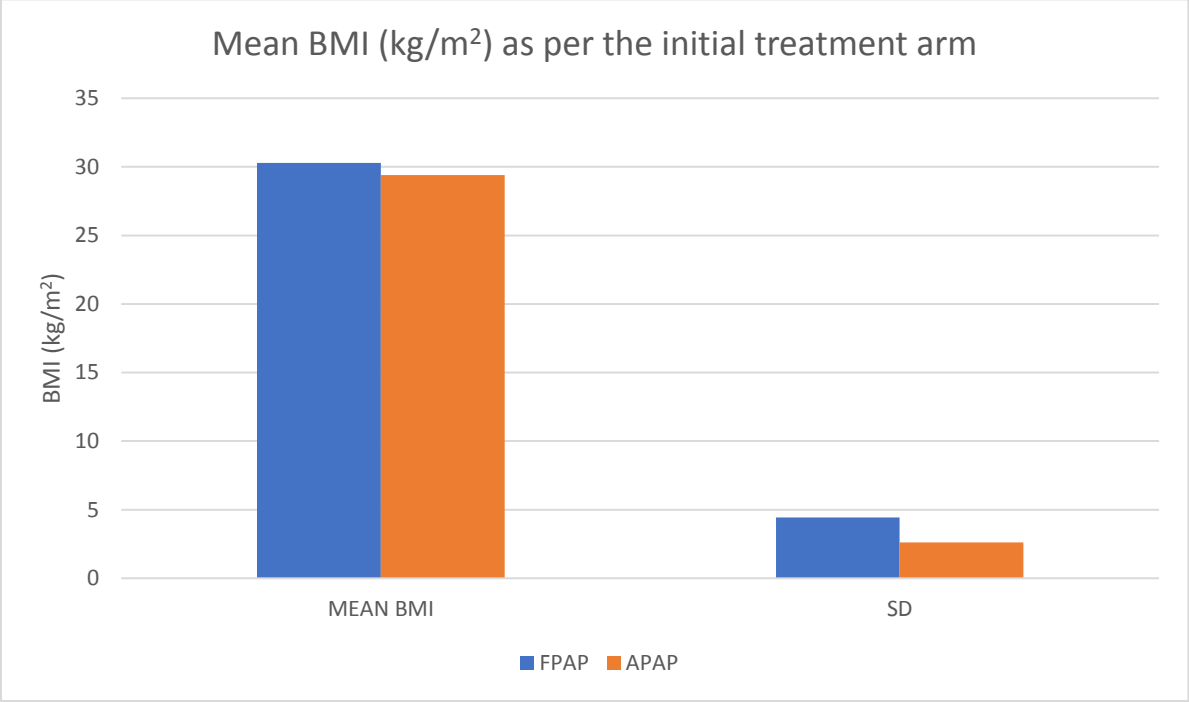




BMI:

The mean BMI of 36 patients was 29.84± 3.62 kg/m^2. In the initial treatment arm, the mean BMI of patients allocated to the FPAP group (n=16) was 30.29± 4.44 kg/m^2 and the APAP group (n=16) was 29.39 ± 2.61 kg/m^2 (p= 0.591).

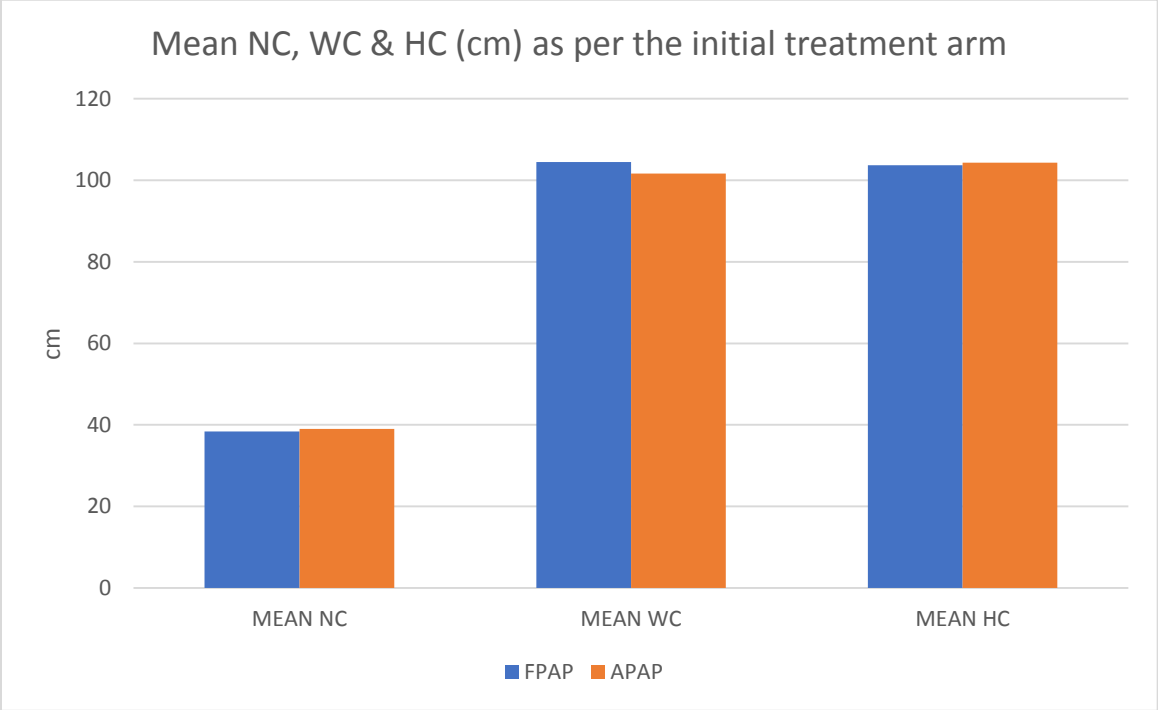
Figure 4: Mean BMI (kg/m^2) between FPAP and APAP as per the initial treatment arm



ANTHROPOMETRIC MEASUREMENTS:

The mean neck circumference (NC), waist circumference (WC) and hip circumference (HC) of 36 patients were 38.69 ± 3.73 cm, 103.06± 8.54 cm and 104.03± 6.75 cm. In the initial treatment arm, the mean neck circumference, waist circumference and hip circumference of patients allocated to the FPAP group (n=16) were 38.39 ± 4.19 cm, 104.50 ± 10.04 cm and 103.72 ± 7.34 cm, respectively and the APAP group (n=16) was 39.00 ± 3.31 cm, 101.61 ± 6.70 cm and 104.33 ± 6.32 cm, respectively (p=0.824, 0.419 and 0.646).

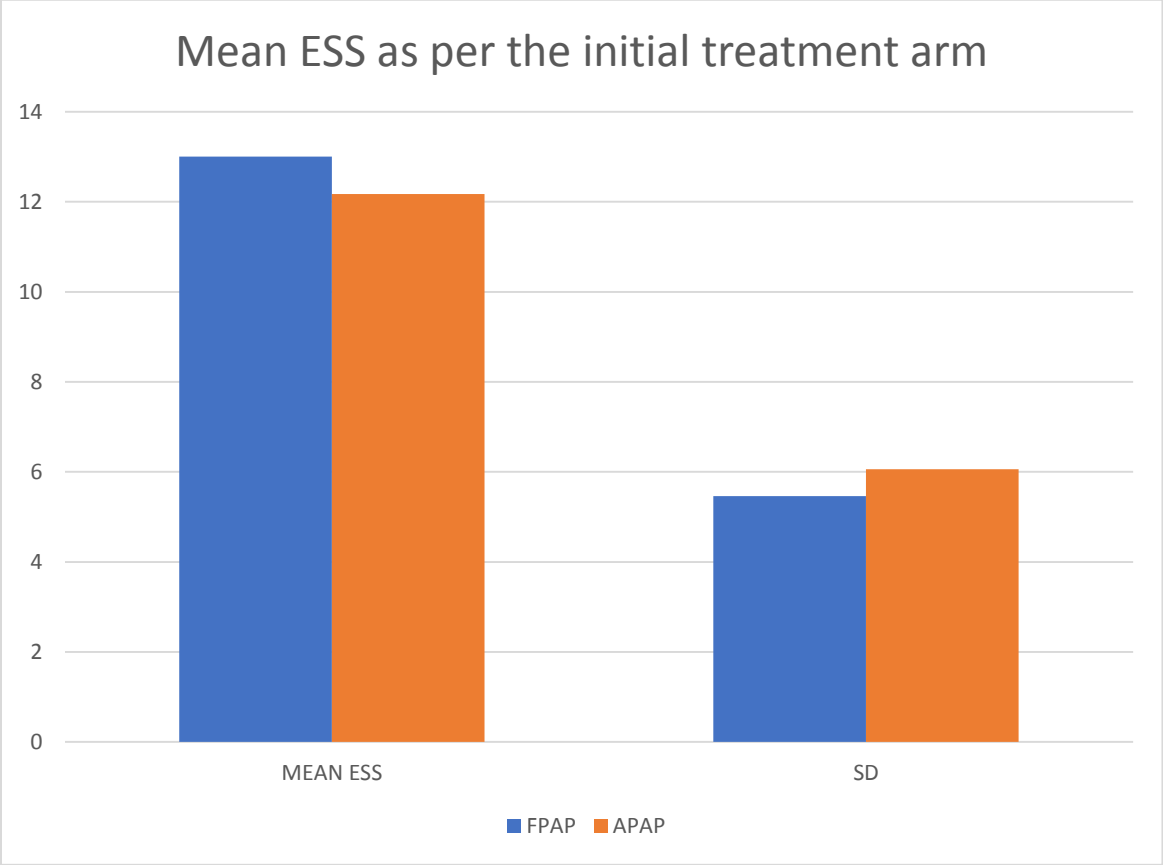
Figure 5: Mean NC, WC & HC (cm) between FPAP and APAP as per the initial treatment arm



DAYTIME SLEEPINESS:

The mean Epworth Sleepiness Score (ESS) of 36 patients was 12.58±5.70. In the initial treatment arm, the mean ESS of patients allocated to the FPAP group (n=16) was 13.00 ± 5.46 and the APAP group (n=16) was 12.17 ± 6.06 (p=0.849).

Figure 6: Mean ESS between FPAP and APAP as per the initial treatment arm



AHI:

The mean AHI of the patients in the study was 66.58 events/hr. In the initial treatment arm, the mean AHI of patients allocated to FPAP group (n=16) was 66.74 ± 31.35 events/hr and APAP group (n=16) was 66.42 ± 34.81 events/hr (p=0.975).

Figure 7: Mean AHI between FPAP and APAP as per the initial treatment arm

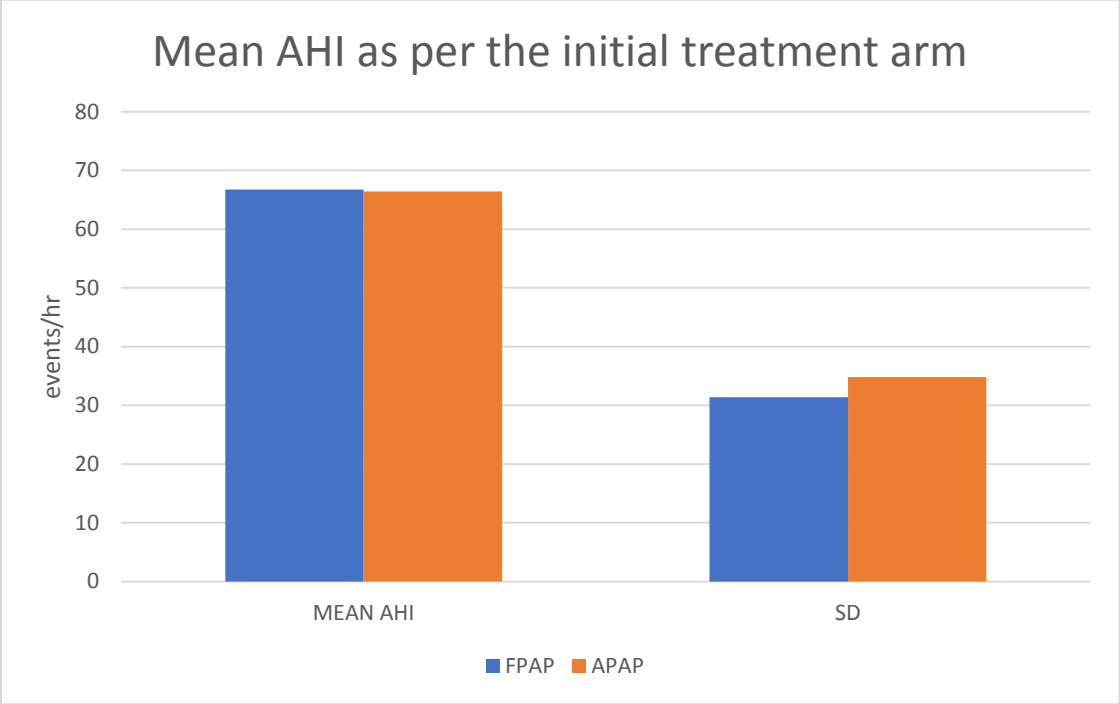


Table 3: Baseline HRV parameters of patients as per the initial treatment arm

Baseline parameter	PAP Therapy	N	Mean	Std Deviation(SD)	p value
Total (milliseconds)	FPAP	18	650.89	685.42	0.164
	APAP	18	1842.61	2003.32	
LFnu (milliseconds^2)	FPAP	18	59.48	17.86	0.743
	APAP	18	57.32	17.27	
HFnu (milliseconds^2)	FPAP	18	40.29	17.47	0.888
	APAP	18	41.73	15.61	
LF/HF	FPAP	18	2.18	1.99	0.791
	APAP	18	1.77	1.24	
RMSSD (milliseconds)	FPAP	18	15.19	9.58	0.181
	APAP	18	22.80	14.82	
pNN50 (%)	FPAP	18	2.37	7.36	0.260
	APAP	18	4.83	8.17	

LFnu: Low Frequency power (millisecond^2), HFnu: High Frequency power (millisecond^2), LF/HF: Low Frequency/High Frequency ratio, RMSSD: Root Mean Square of successive differences between normal heartbeats (millisecond), pNN50: The percentage of adjacent NN intervals that differ from each other by more than 50 ms(%)

In the initial treatment arm the mean total, LFnu, HFnu and LF/HF ratio of patients allocated FPAP (n=18) were 650.89± 685.42, 59.48± 17.86, 40.29± 17.47, 2.18± 1.99 respectively and APAP were 1842± 2003.32, 57.32± 17.27, 41.73± 15.61, 1.77± 1.24 respectively. The difference in mean of the two groups when compared were not statistically significant (p=0.164, 0.743, 0.888, 0.791)

In the initial treatment arm, the mean RMSSD and pNN50 of patients allocated FPAP (n=18) were 15.19± 9.58, 2.37± 7.36 and APAP were 22.80± 14.82, 4.83± 8.17 respectively. The difference in the mean of the two groups when compared were also not statistically significant (p=0.181, 0.260). Thus, both the frequency domain parameters and time domain parameters were matched in both the groups with regard to the first treatment arm they received.

Figure 8: Frequency domain parameters of HRV as per initial treatment arm

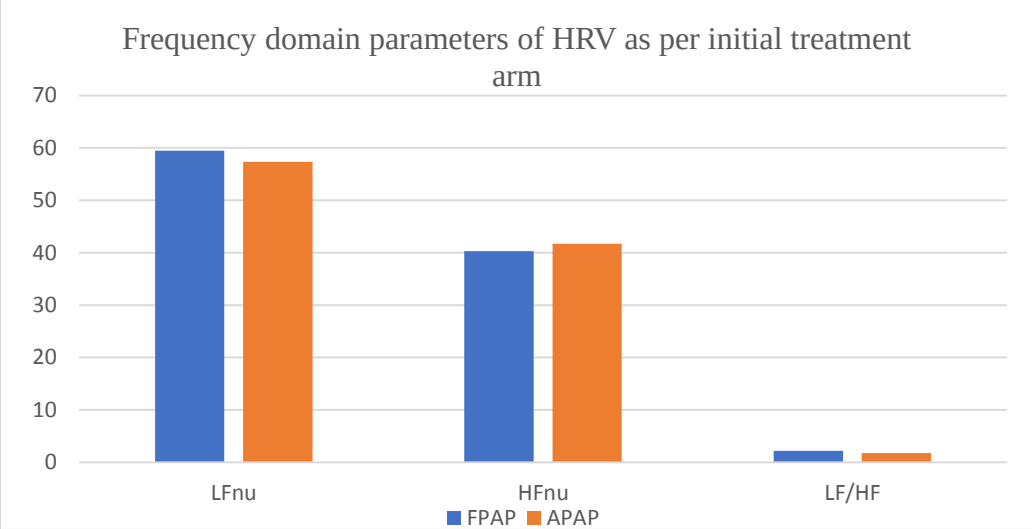


Figure 9: Time domain parameters of HRV as per initial treatment arm

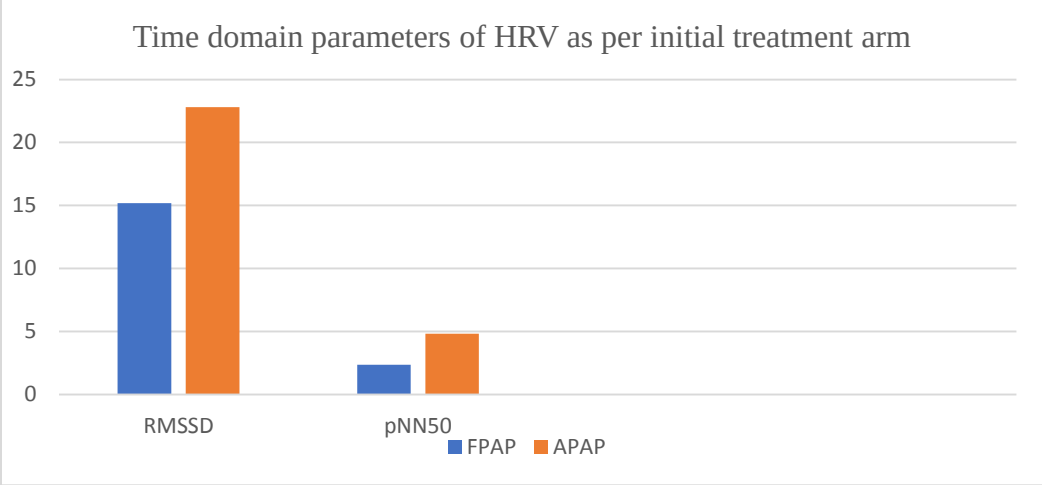


Table 4: Baseline Ewing's battery of Autonomic function test parameters of patients as per the initial treatment arm

Baseline parameter	PAP Therapy	N	Mean	Std Deviation(SD)	p value
S.B.P.	FPAP	18	141.33	20.76	0.788
	APAP	18	143.33	12.39	
D.B.P.	FPAP	18	92.11	15.29	0.799
	APAP	18	92.00	9.20	
H.R.	FPAP	18	80.72	9.90	0.221
	APAP	18	75.78	7.47	
H.R. response to active standing from supine position	FPAP	18	1.03	0.06	0.654
	APAP	18	1.03	0.05	
H.R. response to Valsalva maneuver	FPAP	18	1.40	0.24	0.090
	APAP	18	1.50	0.27	
H.R. response to slow deep breathing	FPAP	18	1.17	0.09	0.145
	APAP	18	1.23	0.11	
B.P. response to sustained handgrip	FPAP	18	10.00	8.89	0.514
	APAP	18	8.44	9.71	
S.B.P. response to active standing from supine position	FPAP	18	-4.22	10.74	0.495
	APAP	18	-8.11	12.43	
D.B.P. response to active standing from supine position	FPAP	18	-2.00	7.00	0.849
	APAP	18	-1.56	5.76	

B.P: Blood Pressure (mm Hg), S.B.P: Systolic Blood Pressure (mm Hg), D.B.P: Diastolic Blood Pressure (mm Hg), H.R: Heart Rate (beats/min).

In the initial treatment arm, the mean S.B.P, D.B.P and H.R of patients allocated FPAP (n=18) were 141.33 mm Hg, 92.11 mm Hg, 80.72 beats/min respectively and APAP were 143.33 mm Hg, 92.00 mm Hg, 75.78 beats/min respectively. The difference in the mean values of the two groups when compared were not statistically significant (p=0.788, 0.799, 0.221).

In the initial treatment arm, the mean heart rate response to active standing from the supine position, heart rate response to the valsalva manoeuvre, and heart rate response to slow deep breathing in patients allocated FPAP (n=18) were 1.03, 1.40, 1.17, respectively and APAP were 1.03, 1.50, 1.23 respectively. The mean values of the two groups when compared and the difference were not statistically significant (p=0.654, 0.09, 0.145).

B.P response to sustained handgrip, S.B.P. response to active standing from the supine position, D.B.P. response to active standing from the supine position in patients allocated FPAP (n=18) were 10.00, -4.22, -2.00 respectively and APAP were 8.44, -8.11, -1.56 respectively. The difference in the mean of the two groups when compared were not statistically significant (p=0.514, 0.495, 0.849).

Figure 10: B.P. and H.R. as per initial treatment arm

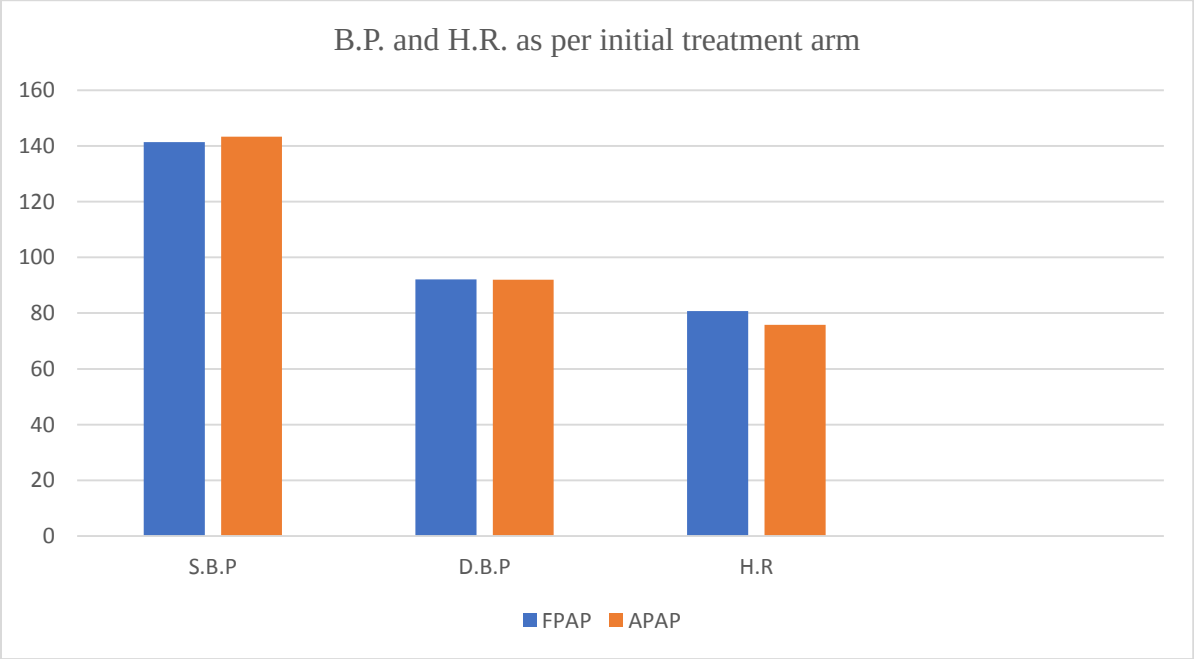
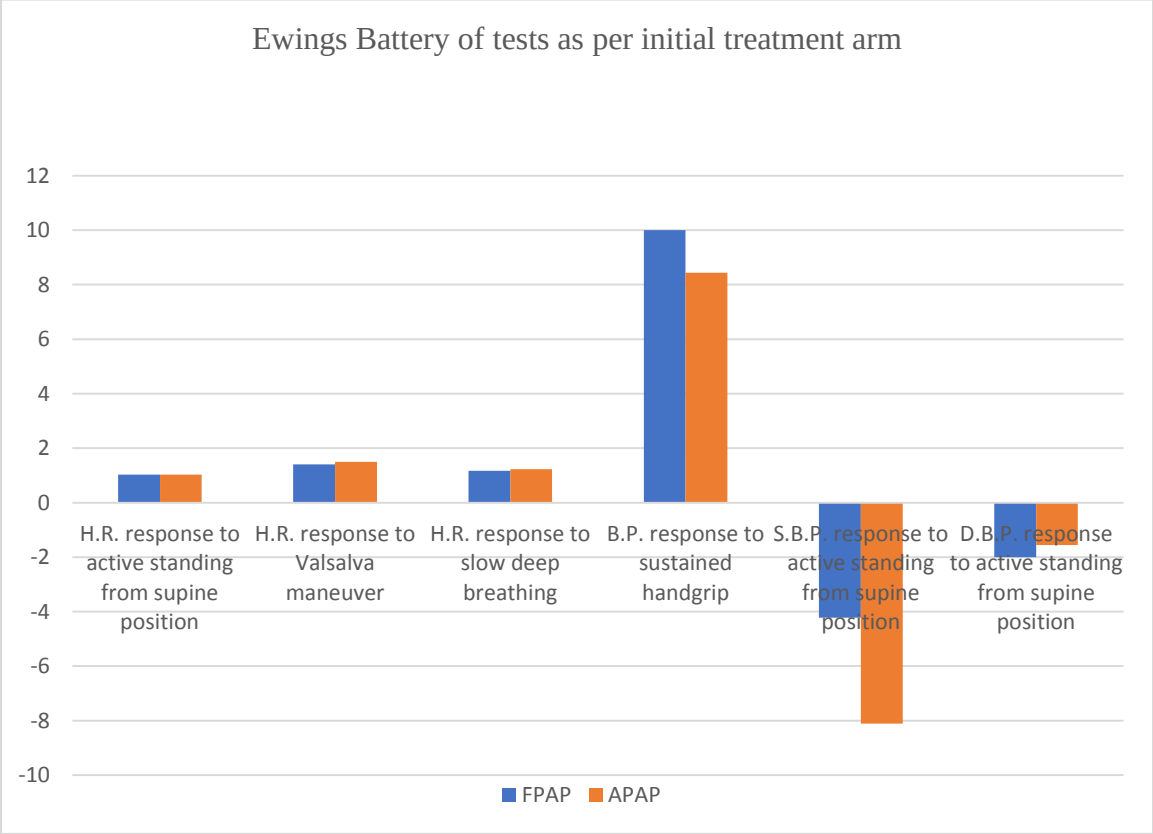


Figure 11: Ewings Battery of tests as per initial treatment arm



CHANGE IN HRV PARAMETERS FROM BASELINE TO 4 WEEKS IN FPAP AND APAP GROUPS

Table 5: Change in HRV parameters after 4 weeks of FPAP

Characteristic	Baseline	4 weeks	Difference	95% CI	P value
Total (millisecond)	1088.5 (1503.9)	1213.1 (1,468.9)	-125	-676, 427	0.647
LFnu (millisecond^2)	61.2 (16.7)	58.3(20.0)	2.9	-5.8, 12	0.501
HFnu (millisecond^2)	38.3 (15.6)	40.2(17.9)	-1.9	-9.7, 5.9	0.623
LF/HF	2.2 (1.7)	2.1(1.9)	0.10	-0.55, 0.75	0.747
RMSSD (millisecond)	16.5 (10.2)	22.5(15.1)	-6.1	-12,-0.52	**0.033**
pNN50 (%)	2.5(5.6)	4.4(8.6)	-1.9	-4.5,0.69	0.144

LFnu: Low Frequency power (millisecond^2), HFnu: High Frequency power (millisecond^2), LF/HF: Low Frequency/High Frequency ratio, RMSSD: Root Mean Square of successive differences between normal heartbeats (millisecond), pNN50: The percentage of adjacent NN intervals that differ from each other by more than 50 ms (%), CI = Confidence Interval

Table 6: Change in HRV parameters after 4 weeks of APAP

Characteristic	Baseline	4 weeks	Difference	95% CI	P value
Total (millisecond)	1088.5 (1503.9)	1110 (948.6)	-22	-577,534	0.937
LFnu (millisecond^2)	61.2 (16.7)	60.2(15.2)	0.99	-7.4,9.4	0.810
HFnu (millisecond^2)	38.3 (15.6)	38.8 (14.7)	-0.54	-8.4, 7.3	0.890
LF/HF	2.2 (1.7)	2.0(1.5)	0.23	-0.33, 0.79	0.405
RMSSD (millisecond)	16.5 (10.2)	19.4(10.2)	-2.9	-6.8,0.88	0.126
pNN50 (%)	2.5 (5.6)	3.1 (5.9)	-0.60	-2.3.1.0	0.460

LFnu: Low Frequency power (millisecond^2), HFnu: High Frequency power (millisecond^2), LF/HF: Low Frequency/High Frequency ratio, RMSSD: Root Mean Square of successive differences between normal heartbeats (millisecond), pNN50: The percentage of adjacent NN intervals that differ from each other by more than 50 ms (%), CI = Confidence Interval

After 4 weeks of FPAP therapy, the mean total value increased from a baseline value of 1088.5 ± 1503.9 to 1213.1 ± 1, 468.9 which is not statistically significant (95% CI: -676, 427, p=0.647). There was a non-significant reduction in LFnu from 61.2 ± 16.7 to 58.3 ± 20.0 (95% CI: -5.8, 12, p=0.501) and increase in HFnu from 38.3 ± 15.6 to 40.2 ± 17.9 (95% CI: -9.7, 5.9, p=0.623). LF/HF ratio at baseline was 2.2 ± 1.7 and it reduced after

four weeks of FPAP to 2.1 ± 1.9 which was not statistically significant (95% CI: -0.55, 0.75, p=0.747). Thus, there was a slight increase in total value, HFnu and a slight decrease in LFnu and LF/Hf ratio after FPAP, but these were not statistically significant.

After 4 weeks of APAP therapy, the mean total value increased from a baseline value of 1088.5 ± 1503.9 to 1110 ± 948.6 which is not statistically significant (95% CI: -577,534, p=0.937). There was a reduction in LFnu from 61.2 ± 16.7 to 60.2 ± 15.2 (95% CI: -7.4,9.4, p=0.810) and a small increase in HFnu from 38.3 ± 15.6 to 38.8 ± 14.7 (95% CI: -8.4, 7.3, p=0.890) which were not significant. LF/HF ratio at baseline was 2.2 ± 1.7 and it reduced after four weeks of FPAP to 2.0 ± 1.5, which was not statistically significant (95% CI: -0.33, 0.79, p=0.405). Thus, there was a slight increase in total value, HFnu and a slight decrease in LFnu and LF/HF ratio after APAP also, which was not statistically significant.

Figure 12: Change in frequency domain parameters after FPAP

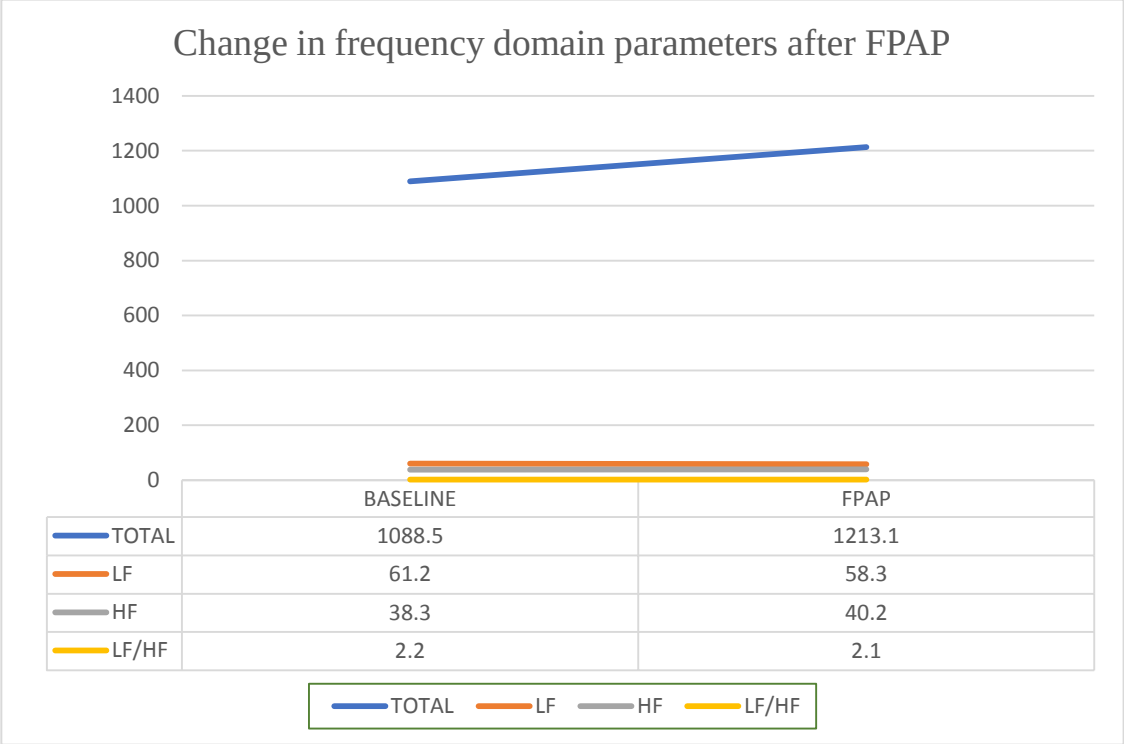
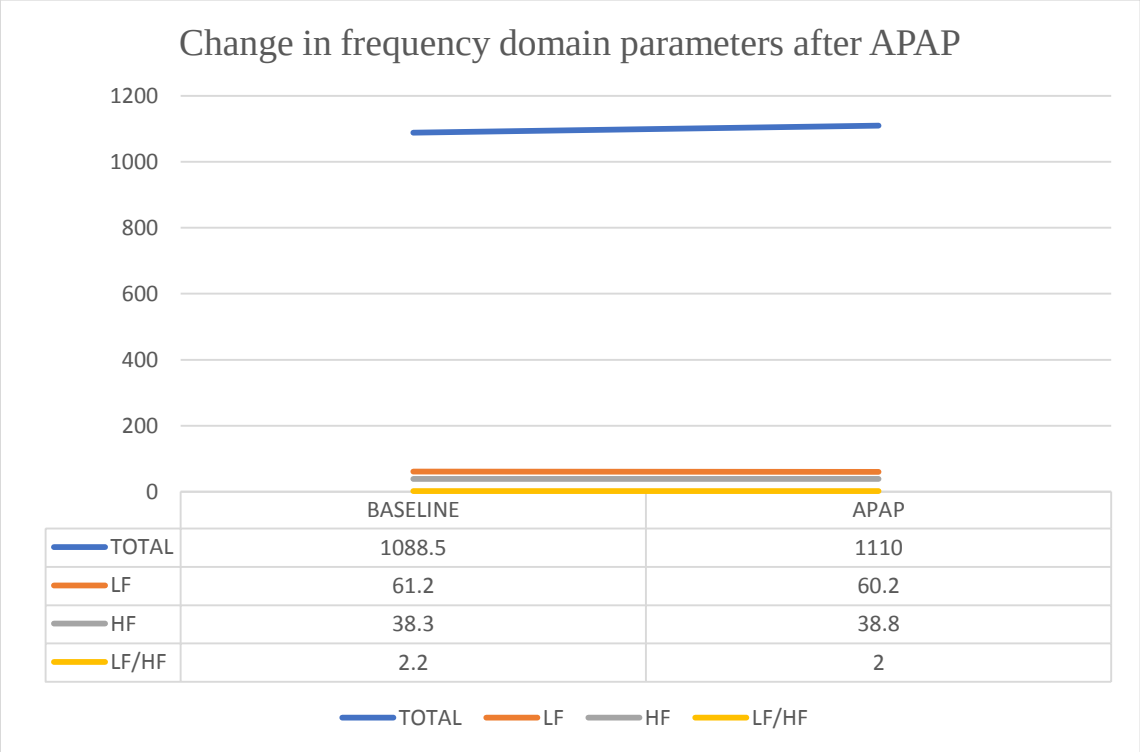


Figure 13: Change in frequency domain parameters after APAP



The mean RMSSD increased from a baseline value of 16.5 ± 10.2 to 22.5 ± 15.1 after 4weeks of FPAP. The change was statistically significant (95%CI: -6.8,0.88, p= 0.033). The pNN50 at the baseline was 2.5 ± 5.6 and after four weeks of FPAP it increased from 4.4 ± 8.6. However, the change was not statistically significant (95%CI: -2.3.1.0, p = 0.144).

The mean RMSSD and pNN50 increased from a baseline value of 16.5 ± 10.2 to 19.4 ± 10.2 (95%CI: -6.8,0.88, p= 0.126) and from 2.5 ± 5.6 to 3.1 ± 5.9 (95%CI: -2.3.1.0, p = 0.460) after 4weeks of APAP therapy. The increase was, however, not statistically significant.

Thus statistical improvement in HRV analysis was seen only in RMSSD with 4 weeks of FPAP therapy.

Figure 14: Change in time domain parameters after FPAP

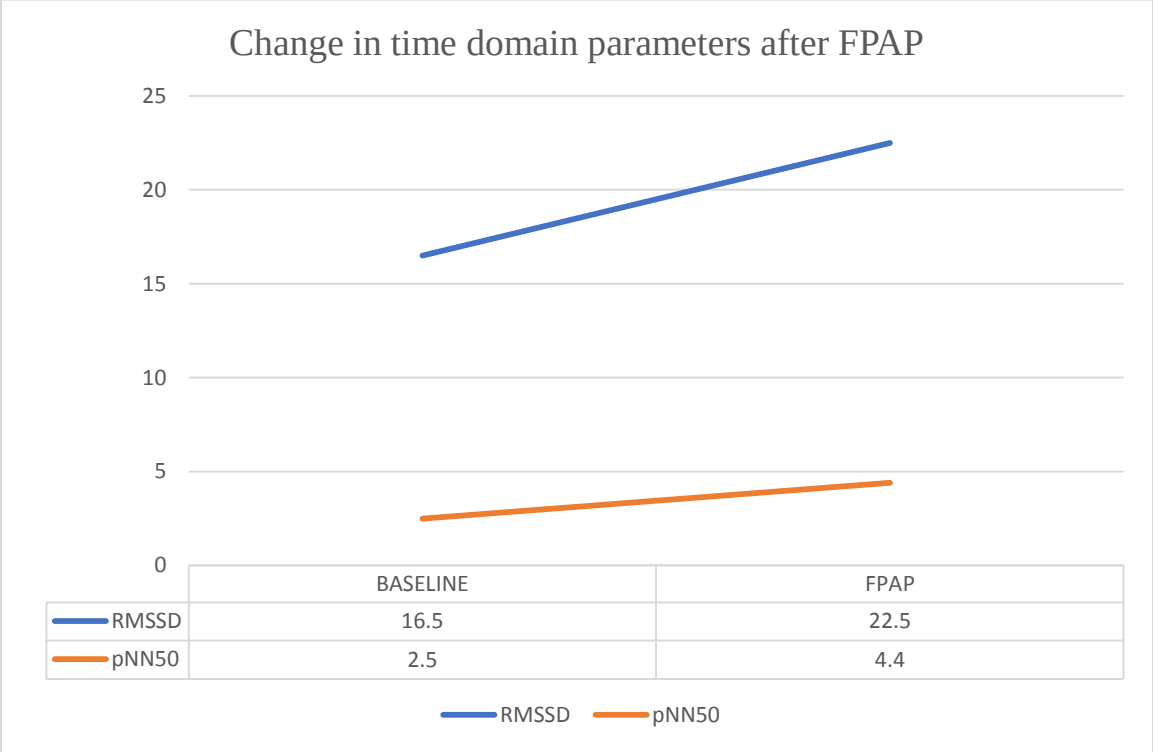


Figure 15: Change in time domain parameters after APAP

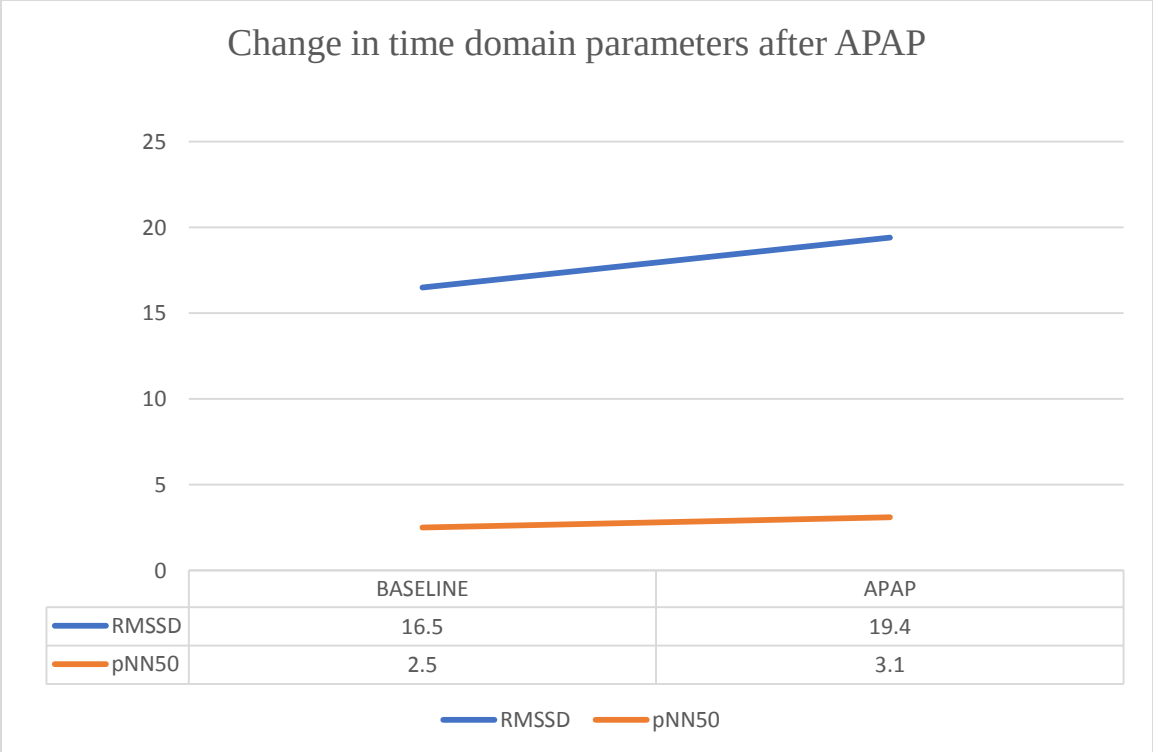


Table 7: Change in Ewing's battery of Autonomic function test parameters after 4 weeks of FPAP

Characteristic	Baseline	4 weeks	Difference	95% CI	P value
S.B.P	143.9(16.0)	133.1(15.7)	11	5.3,16	**<0.001**
D.B.P	92.9(12.6)	90.5(23.2)	2.4	-5.8,11	0.552
H.R	79.0(9.5)	74.6(9.1)	4.4	0.91,7.8	**0.015**
Heartrate response to active standing from supine position	1.0(0.1)	1.0(0.1)	0.02	-0.02,0.06	0.356
Heartrate response to Valsalva maneuver	1.5(0.3)	1.5(0.2)	-0.05	-0.14,0.04	0.298
Heartrate response to slow deep breathing	1.2(0.1)	1.2(0.1)	-0.01	-0.06,0.04	0.645
B.P. response to sustained handgrip	8.7(7.7)	9.8(8.5)	-1.1	-5.6,3.5	0.635
S.B.P. response to active standing from supine position	-7.5(11.6)	-3.4(4.5)	-4.0	-9.1,0.99	0.111
D.B.P. response to active standing from supine position	-1.9(6.1)	-0.1(7.0)	-1.9	-5.4,1.6	0.285

B.P: Blood Pressure (mm Hg), S.B.P: Systolic Blood Pressure (mm Hg), D.B.P: Diastolic Blood Pressure (mm Hg), H.R: Heart Rate (beats/min), CI: Confidence Interval.

Table 8: Change in Ewing's battery of Autonomic function test parameters after 4 weeks of APAP

Characteristic	Baseline	4 weeks	Difference	95% CI	P value
S.B.P	143.9 (16.0)	132.3 (16.3)	12	6.1,17	**<0.001**
D.B.P	92.9 (12.6)	87.9 (13.3)	5.0	1.4,8.6	**0.008**
H.R.	79.0 (9.5)	77.0 (7.0)	2.0	-0.99,5.0	0.182
Heartrate response to active standing from supine position	1.0 (0.1)	1.0 (0.0)	0.02	-0.01,0.05	0.117
Heartrate response to Valsalva maneuver	1.5 (0.3)	1.5 (0.3)	-0.05	-0.14, 0.04	0.283
Heartrate response to slow deep breathing	1.2 (0.1)	1.2 (0.1)	-0.01	-0.05, 0.03	0.664
B.P. response to sustained handgrip	8.7 (7.7)	9.1 (7.2)	-0.40	-3.6, 2.8	0.802
S.B.P. response to active standing from supine position	-7.5(11.6)	-1.6 (6.4)	-5.9	-11,-0.49	0.034
D.B.P. response to active standing from supine position	-1.9(6.1)	0.5(5.9)	-2.4	-4.7, -0.12	0.040

B.P: Blood Pressure (mm Hg), S.B.P: Systolic Blood Pressure (mm Hg), D.B.P: Diastolic Blood Pressure (mm Hg), H.R: Heart Rate (beats/min), CI: Confidence Interval.

With 4 weeks of FPAP therapy, S.B.P decreased from a baseline value of 143.9 ± 16.0 mm Hg to 133.1 ± 15.7 mm Hg, which was a statistically significant reduction (95%CI: 5.3,16, p<0.001) and D.B.P decreased slightly from 92.9 ± 12.6 mm Hg to 90.5 ± 23.2, mm Hg however statistically not significant (95%CI: -5.8,11,p=0.552). H.R. reduced from 79.0 ± 9.5 beats/min to 74.6 ± 9.1 beats/min after 4 weeks of FPAP. The decrease was statistically significant (95%CI: 0.91,7.8, p=0.015).

There was negligible change in heart rate response to active standing from the supine position from a baseline value of 1.00 ± 0.1 to 1.00 ± 0.1 (95%CI: -0.02,0.06, p= 0.356). There was a slight decrease in both heart rate response to the Valsalva manoeuvre and slow deep breathing from baseline values of 1.5 ± 0.3 and 1.2 ± 0.1 to 1.5 ± 0.2 (95%CI: -0.14,0.04, p=0.298) and 1.2 ± 0.1 (95%CI: -0.06,0.04, p= 0.645) respectively after 4 weeks of FPAP therapy.

B.P. response to sustained handgrip at baseline was 8.7 ± 7.7 and it increased to 9.8 ± 8.5 after 4 weeks of FPAP, which was not statistically significant (95%CI: -5.6,3.5, p=0.635). S.B.P. and D.B.P response to active standing from supine position changed from the baseline values of -7.5 ± 11.6 and -1.9 ± 6.1 to -3.4 ± 4.5 (95%CI: -9.1,0.99,p=0.111) and -0.1 ± 7.0 (95%CI: -5.4,1.6,p=0.285) respectively, which is not statistically significant.

Thus, there was no statistically significant improvement in Ewings battery of tests with 4 weeks of FPAP therapy. Only S.B.P and H.R. showed statistically significant improvement.

Figure 16: Change in B.P. and H.R. after FPAP

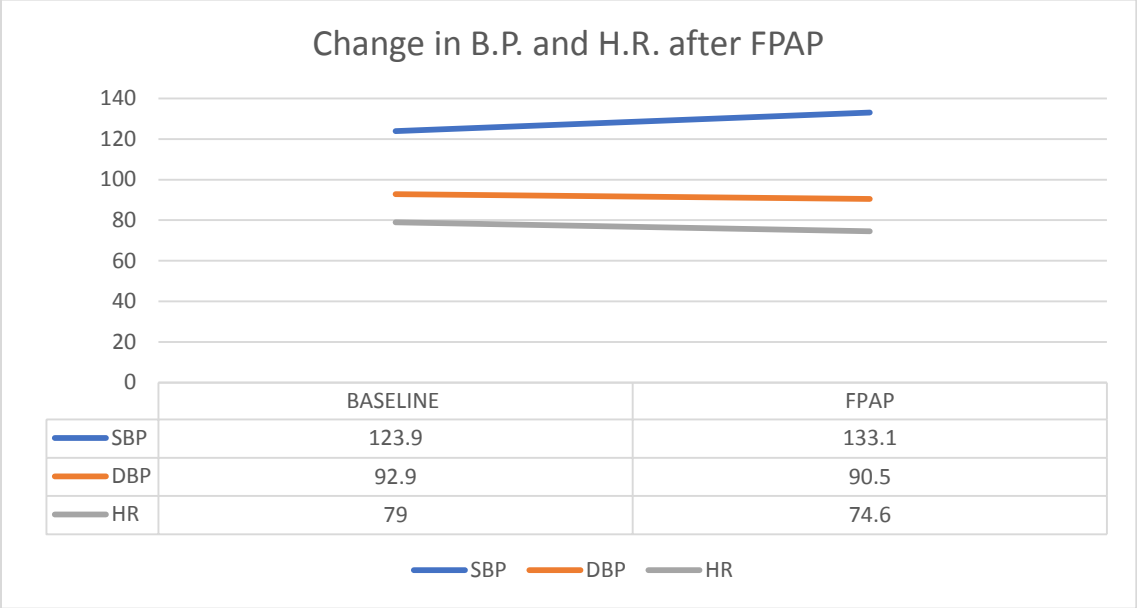
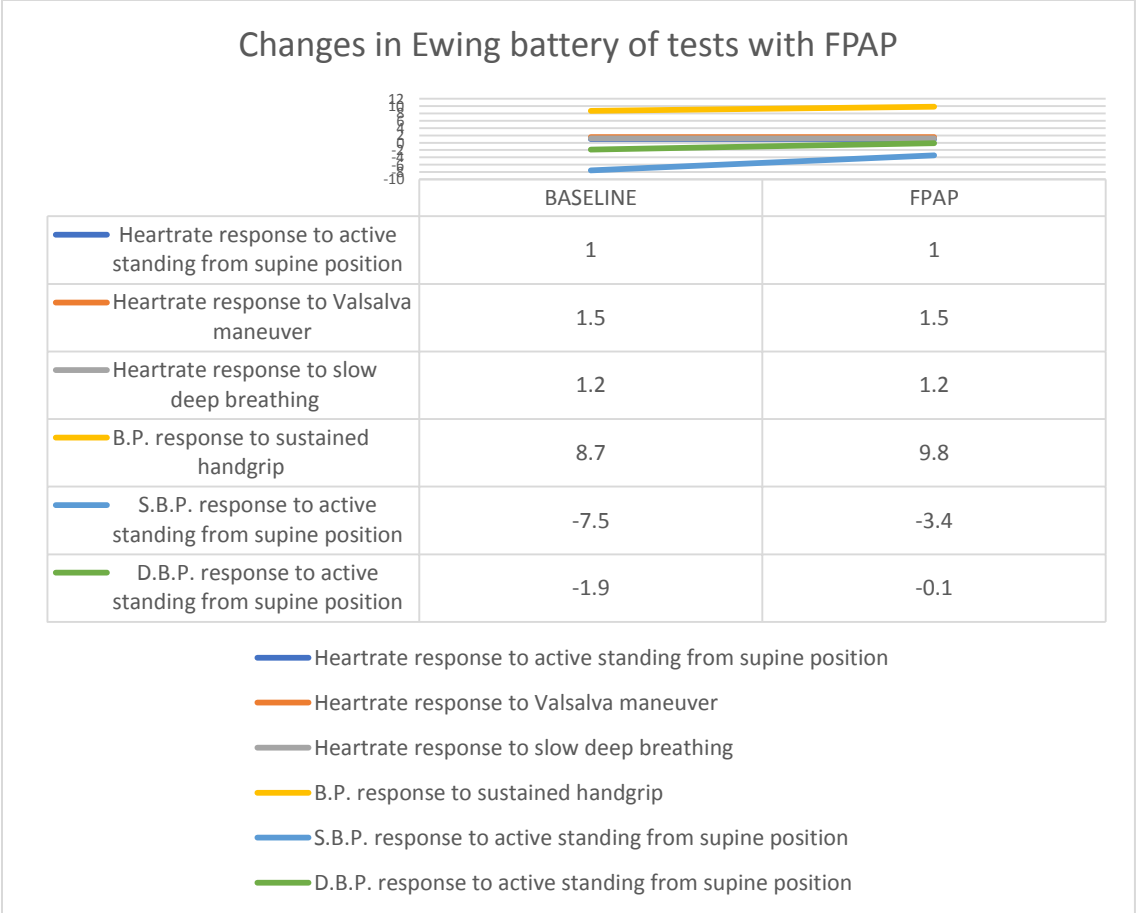


Figure 17: Changes in Ewing battery of tests with FPAP



With 4 weeks of APAP therapy, there was a statistically significant reduction in S.B.P and D.B.P. S.B.P decreased from the baseline value of 143.9 ± 16.0 mm Hg to 132.3 ± 16.3 mm Hg (95%CI: 6.1,17, p<0.001) and D.B.P decreased from 92.9 ± 12.6 mm Hg to 87.9 ± 13.3 mm Hg (95%CI: -1.4,8.6, p=0.008). H.R. reduced from 79.0 ± 9.5 beats/min to 77.0 ± 7 beats/min after 4 weeks of APAP. The decrease was not statistically significant (95%CI: -0.99,5.0, p=0.182).

There was minimal change in heart rate response to active standing from the supine position from a baseline value of 1.00 ± 0.1 to 1.00 ± 0.1 with a difference of 0.02, which was statistically not significant (95%CI: -0.12,0.05, p= 0.117). There was a slight decrease in both heart rate response to the Valsalva manoeuvre and slow deep breathing from baseline values of 1.5 ± 0.3 and 1.2 ± 0.1 to 1.5 ± 0.3 (95%CI: -0.14, 0.04, p=0.283) and 1.2 ± 0.1 (95%CI: -0.05,0.03, p= 0.664) after 4 weeks of APAP therapy with a difference of 0.05 and 0.01 respectively and the changes were not statistically significant.

B.P. response to sustained handgrip at baseline was 8.7 ± 7.7 and it increased to 9.1 ± 7.2 after four weeks of FPAP, which was not statistically significant (95%CI: -3.6,2.85, p=0.802). S.B.P and D.B.P response to active standing from a supine position changed from the baseline value of -7.5 ± 11.6 and -1.9 ± 6.1 to -1.6 ± 6.4 (95%CI: -11,-0.49, p=0.034) and 0.5 ± 5.9 (95%CI: -4.7, -0.12, p=0.040) respectively, which were statistically significant.

Thus, S.B.P, D.B.P and only two out of six components of the Ewings battery of tests: S.B.P and D.B.P response to active standing from the supine position, showed statistically significant improvement with 4 weeks of APAP therapy.

Figure 18: Change in B.P. and H.R. after APAP

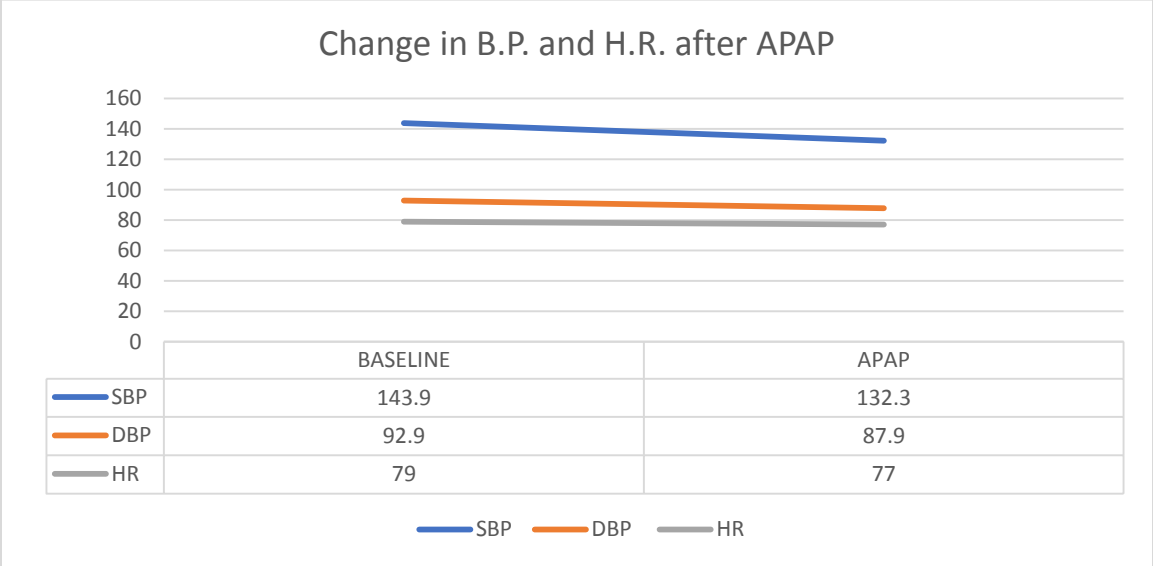
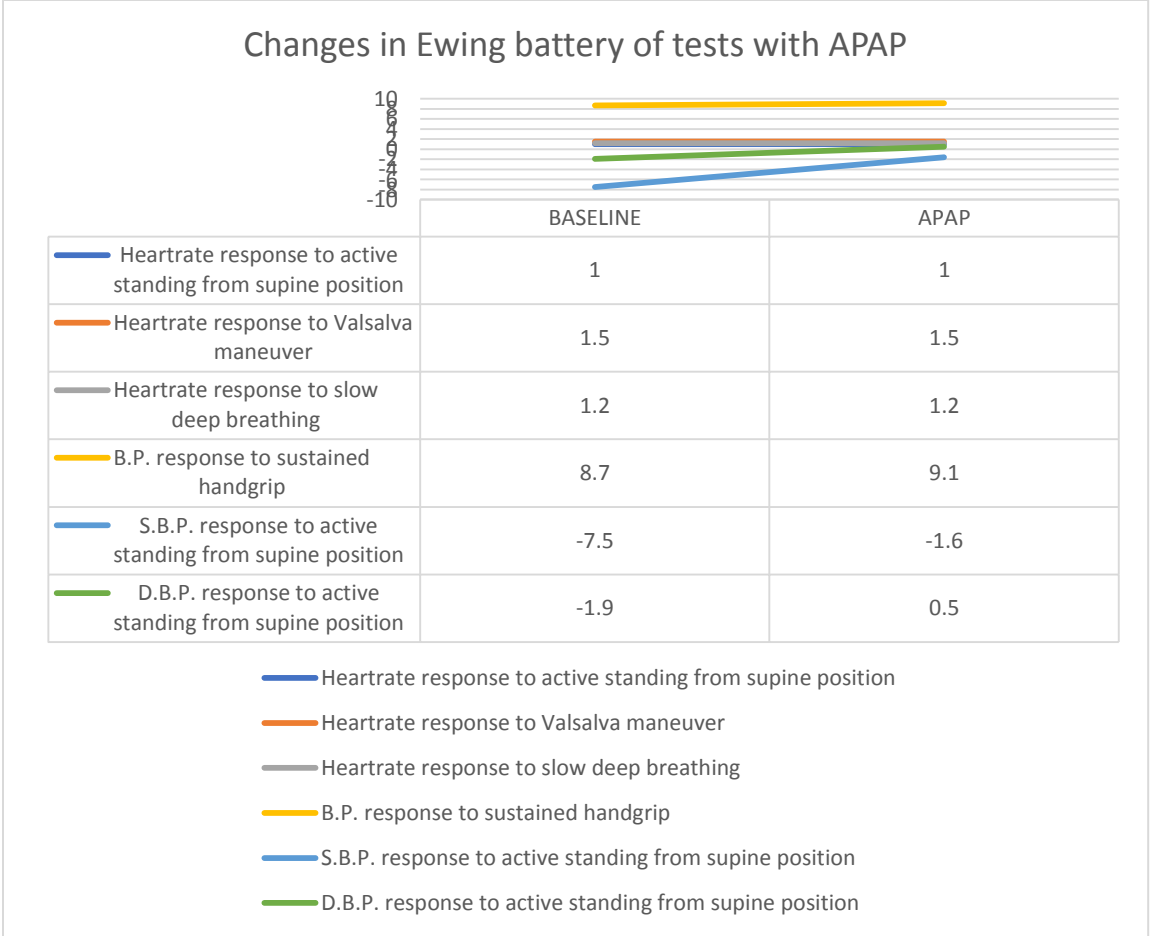


Figure 19: Changes in Ewing battery of tests with APAP



IMPROVEMENT IN AHI FROM BASELINE WITH FPAP AND APAP:

The mean AHI at diagnosis during the titration study was 63.73 events/hr and with four weeks of FPAP and APAP therapy was 1.30 events/hr and 1.38 events/hr respectively.

COMPARISON OF DAYTIME SLEEPINESS (ESS), FATIGUE (FATIGUE SEVERITY SCALE) AND SLEEP QUALITY OF LIFE (PSQI) BETWEEN FPAP AND APAP

The mean ESS, FSS and PSQI at baseline were 11.63, 36.33, and 8.55. The mean ESS, FSS and PSQI after FPAP were 4.5, 26.50 and 5.69 and after APAP were 5.3, 26.07 and 5.76 respectively with p-values <0.001 in all the scores.

Table 9: Comparison of ESS, FSS and PSQI scores between FPAP and APAP

	Baseline	**FPAP**	**APAP**	**95% CI**	**Bayes Factor**	**p value**
ESS	11.63	4.5	5.3	0.14,1.00	-17.78	<0.001
FSS	36.33	26.50	26.07	0.65,0.80	-8.21	<0.001
PSQI	8.55	5.69	5.76	0.03,1.00	-11.98	<0.001

Figure 20: Comparison of ESS from baseline with FPAP and APAP

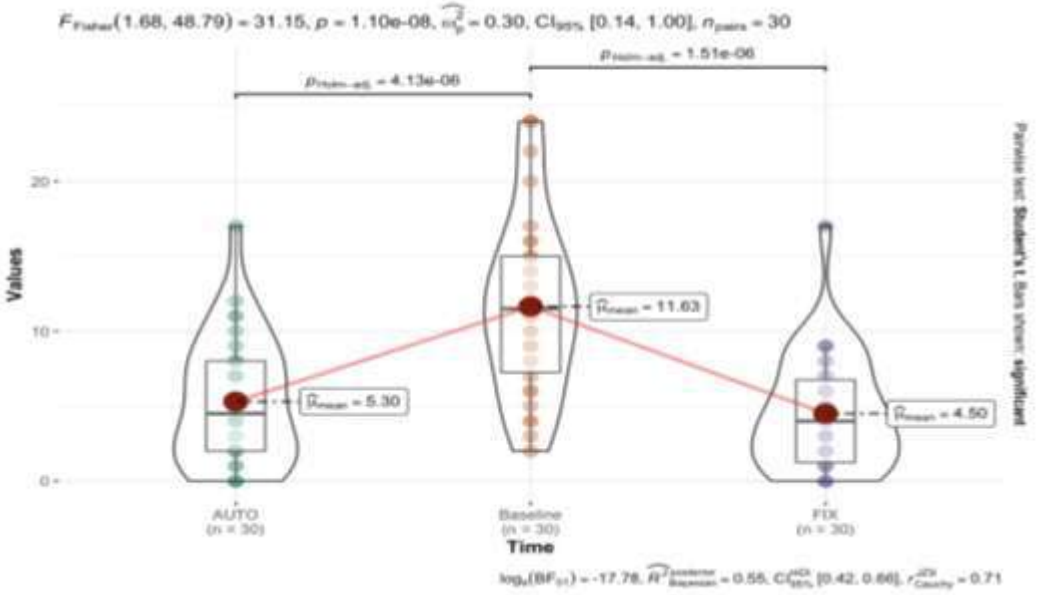


Figure 21: Comparison of FSS from baseline with FPAP and APAP

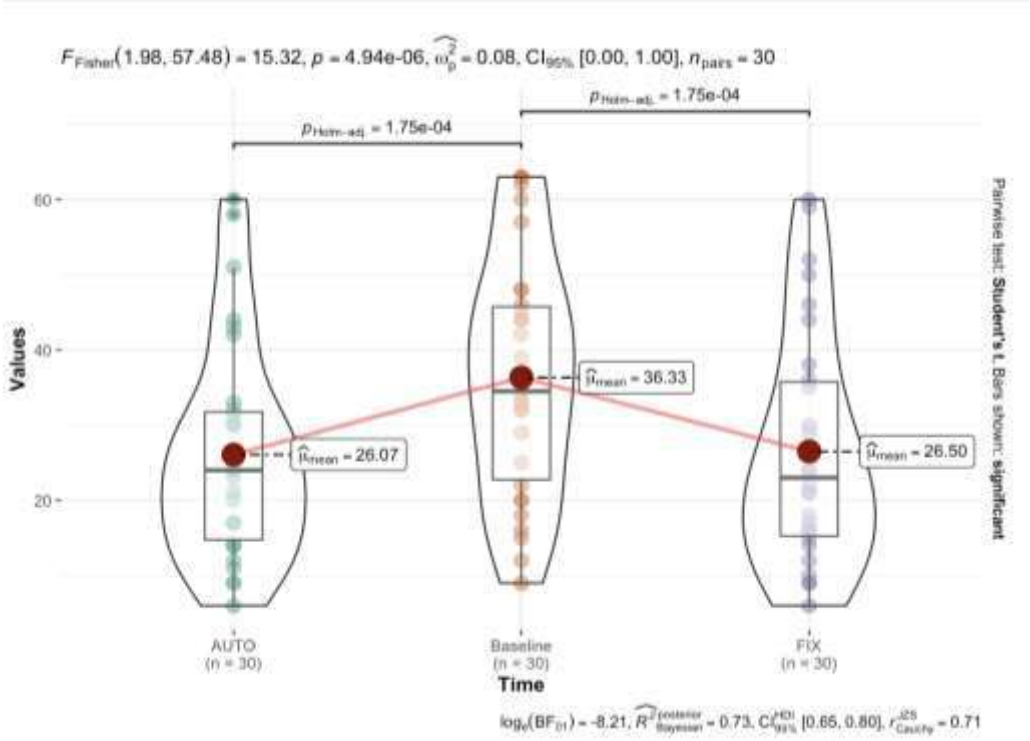
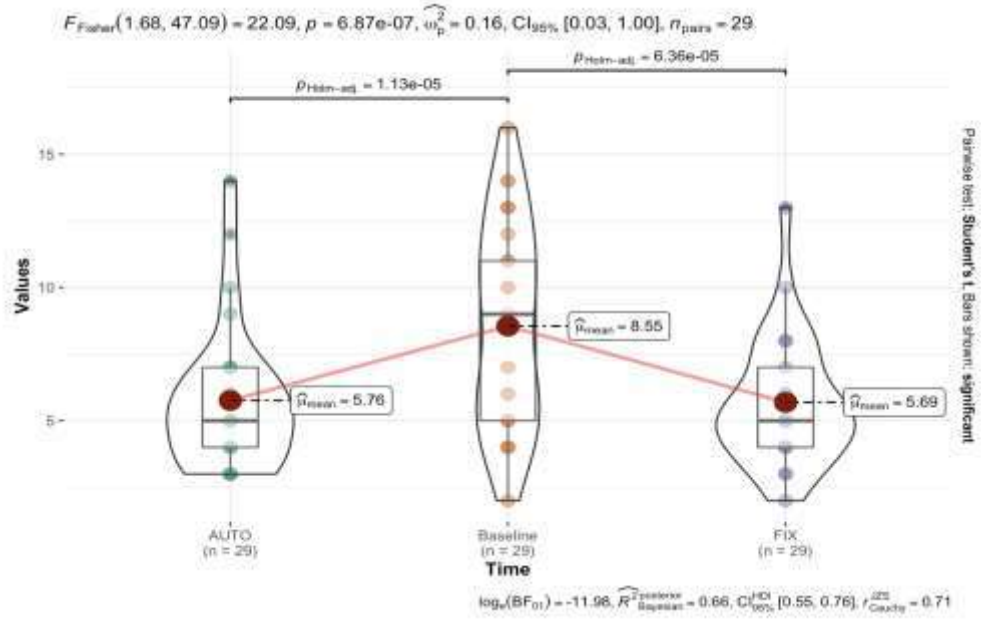


Figure 22: Comparison of PSQI from baseline with FPAP and APAP



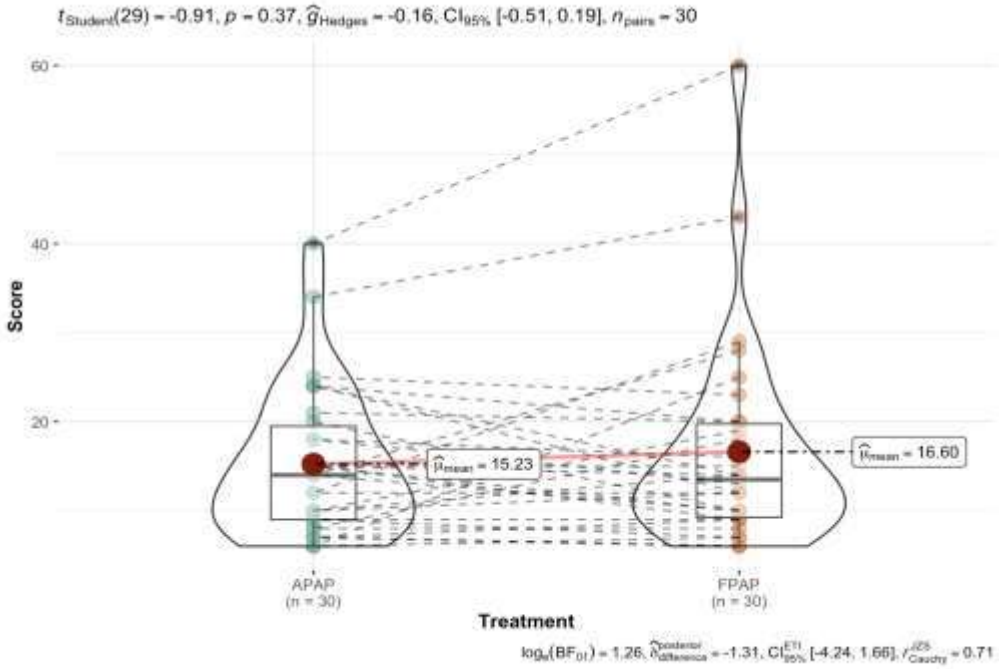
COMPARISON OF PAP QUESTIONNAIRE SCORE AFTER FPAP AND APAP THERAPY

The mean PAP questionnaire score of all the patients after using FPAP was 16.60 and after using APAP was 15.23. Although APAP had a lesser score as compared to FPAP, this difference was not statistically significant (p=0.37). The effect size is small and non-significant, calculated using Hedges' g (-0.61) with a CI 95% of -0.51,0.19.

Table 10: Differences in PAP questionnaire after FPAP and APAP

Type		Mean	95% CI for Hedges' g	p value	Hedges' g
PAP questionnaire score	FPAP	16.60	-0.51,0.19	0.37	-0.16
	APAP	15.23			

Figure 23: Differences in PAP questionnaire after FPAP and APAP



COMPARISON OF MEAN PRESSURES BETWEEN FPAP AND APAP

Out of the total 30 patients who were finally analysed, 25 patients were titrated with CPAP and 5 with BiPAP. The mean PAP pressures achieved during manual titration and given through FPAP (patients who received BiPAP, mean of IPAP and EPAP included) was 12.51 ± 4.55 cm H2O. The mean APAP pressure ≥ 95% of the time for 4 weeks was 10.33 ± 2.66 cm H2O. The difference in pressure between the two groups was statistically significant (p=0.028).

Table 11: Comparison of Mean pressures (cm of H2O) of FPAP and APAP

	Mean pressure in cm of H2O (SD)	**p value**
Average FPAP pressure (cm of H2O)	12.51 (4.55)	0.028
Average APAP pressure ≥ 95% of the time in 4 weeks (cm of H2O)	10.33 (2.66)	

DISCUSSION

Obstructive sleep apnea (OSA) is a common disease associated with several cardiovascular diseases. OSA patients have altered autonomic function[67–69]. Adverse effects associated with OSA also include increased sympathetic activity, systemic inflammation, and metabolic dysregulation[70]. Cardiovascular morbidity and hypertension in moderate to severe OSA patients are attributed to autonomic abnormalities[71,72]. The relationship between the autonomic nervous system and OSA is not unidirectional. Autonomic derangement may contribute to the worsening of OSA[73]. OSA patients, if not treated, are prone to develop cardiovascular disease[74,75]. Positive airway pressure is the gold standard treatment for OSA[76]. However, in OSA patients, the autonomic system response to continuous positive airway pressure depends on the duration of the therapy[77–79]. The degree of improvement in cardiac autonomic functions varied in different studies, which were also dependent on the type of PAP therapy used, the duration of therapy, the method of PAP titration and the method of assessment of the autonomic nervous system[21,38,51,52]. Hence, in the present study, we compared the effect of FPAP and APAP on cardiac autonomic functions in moderate to severe OSA patients, diagnosed by using in-lab manual titration to determine the FPAP pressures.

There are limited studies assessing the changes in autonomic functions with PAP therapy in OSA patients by using HRV parameters and Ewings battery of tests. This is a novel study of the kind to our best knowledge, which is a randomised crossover study to compare the effects of FPAP vs APAP on improvement in cardiac autonomic function in moderate to severe OSA patients. In the present study, patients were divided into two

groups, CPAP and APAP groups, who matched with respect to age, BMI, gender, daytime sleepiness, quality of sleep questionnaires, and PSG parameters and were crossed over after four weeks of CPAP to APAP and vice versa after a washout period of 2 weeks between the two arms. Cardiac autonomic functions assessment was done by HRV and Ewing's battery of tests in the morning to avoid variation in circadian rhythm and to assess sustained autonomic system improvement.

Comparison of changes in HRV parameters by FPAP and APAP

The total HRV represents the overall variability in heartbeat intervals encompassing all frequencies of HRV, including sympathetic and para-sympathetic contributions. Higher total HRV indicates good autonomic balance and lower total HRV indicates stress and autonomic imbalance. Total HRV showed a slight increase from baseline to 4 weeks of treatment with both FPAP (1088.5 ± 1503.9 to 1213.1 ± 1468.9) and APAP (1088.5 ± 1503.9 to 1110 ± 948.6). Though the increase in the value was not statistically significant, it shows improvement in overall heart rate variability with four weeks of treatment with both FPAP and APAP. The wide confidence intervals suggest considerable variability in response among the patients. LF component reflects both sympathetic and parasympathetic activity with dominance of sympathetic activity and HF reflects parasympathetic activity. The LFnu value decreased slightly by 2.9 from the baseline value of 61.2 ± 16.7 to 58.3 ± 320.0 at 4 weeks of FPAP and the HFnu value increased by 1.9 from a baseline value of 38.3 ± 15.6 to 40.2 ± 17.9 after 4 weeks of FPAP therapy. The change in LFnu and HFnu values was not statistically significant. With APAP therapy LFnu decreased slightly from the baseline value of 61.2 ± 16.7 to 60.2 ± 19.9 with a difference of 0.99 and HFnu was 38.3 ± 15.6 at baseline and 38.8 ± 14.7 after four

weeks of APAP which was almost similar. Thus, there is a non-significant decrease in sympathetic and increased parasympathetic activity with four weeks of therapy with both FPAP and APAP. The LF/HF ratio signifies a balance between sympathetic and para-sympathetic activity. A high LF/HF ratio indicates sympathetic overactivity or parasympathetic withdrawal and a low ratio indicates parasympathetic overactivity. LF/HF ratio was 2.2 ± 1.7 at baseline, reduced to 2.1 ± 1.9 after four weeks of FPAP and to 2.0 ± 1.5 at four weeks follow up after APAP therapy, resulting in no statistically significant improvement. The normal LF/HF ratio is 1.5 - 2.0 and the baseline was in the normal range of 2.2 ± 1.7, which signifies the cardiac autonomic function of the patients in the study was relatively balanced at baseline and so with treatment.

The time domain parameters assessed in the study were RMSSD and pNN50. RMSSD is a key indicator of short-term HRV and is a marker of parasympathetic activity. RMSSD at baseline was 16.5 ± 10.2. It increased to 22.6 ± 15.1 (p-value= 0.033) with FPAP therapy and 19.4 ± 10.2 with four weeks of APAP. RMSSD showed statistically significant improvement after four weeks of FPAP, thus signifies the improvement in parasympathetic cardiac activity by enhancing vagal tone. pNN50 is also an indicator of parasympathetic activity. pNN50 increased from 2.5 ± 5.6 to 4.4 ± 8.6 with four weeks of FPAP therapy and from 2.5 ± 5.6 to 3.1 ± 5.9 after four weeks of APAP therapy, indicating mild improvement in parasympathetic activity with both FPAP and APAP therapy, which was not statistically significant.

Thus, intervention with both FPAP and APAP did not result in a significant change in most of the HRV parameters except RMSSD with FPAP.

In a study conducted by Pimporn Limphanudom MD et al[21] in ten moderate to severe OSA patients, LFnu, HFnu, LF/HF ratio and SDNN were measured at one, three- and six-months treatment with CPAP in the daytime. Only SDNN during deep breathing improved in 7 out of 10 patients after six months of treatment with CPAP. Frequency domain parameters that include LFnu, HFnu, and LF/HF ratio were not affected. During the nocturnal assessment of HRV by Levent Karasulu et al[51]comparing acute effects on HRV parameters by CPAP and APAP in severe OSA patients, it found that LF, nuLF, nuHF and LF/HF values in stage 2 improved with CPAP and not with APAP and there was no statistical difference in RMSSD and SDAAN values. In a full night polysomnographic HRV assessment study on CPAP and APAP on autonomic regulation along with controls, it found that CPAP and control groups, LFnu and LF/HF decreased from N2 to N3 and increased during REM sleep while in APAP group, sympathetic modulation was significantly higher compared to those of CPAP and control groups during all the stages of sleep[38]. In another study assessing the short-term and long-term impact of CPAP therapy on HRV parameters during sleep and wakefulness, it was found that both acute and chronic CPAP therapy decreased LF power and increased HF power during NREM and REM and decreased LF/HF ratio during REM. However, a decrease in LF/HF ratio was observed during NREM only after chronic CPAP use. No differences were observed during wakefulness. They concluded that long-term CPAP treatment is needed in OSA patients to increase para-sympathetic modulation of the heart both in the NREM and REM phases of sleep and hence reduce the sympathovagal imbalance with the potential to decrease the risk of death.

In a study on overweight severe OSA patients by Quadri F et al with two months of CPAP, there was an increase in the HF power component and a decrease of both the LF power component and LF/HF ratio was observed. However, the study was done only in 12 obese OSA patients, so it cannot be generalised to all OSA patients.

Comparison of changes in Ewings battery of tests by FPAP and APAP

Ewings battery of tests includes heart rate response to active standing from supine, heart rate response to Valsalva manoeuvre, heart rate response to slow deep breathing, B.P. response to sustained handgrip, S.B.P. response to active standing from supine position D.B.P. response to active standing from the supine position. Before assessing the Ewings battery of tests, patients' resting H.R, S.B.P and D.B.P were calculated.

Blood pressure is one of the key indicators of cardiovascular function. With 4 weeks of FPAP therapy, there was a statistically significant (p-value <0.001) decrease in systolic blood pressure by 11 mm Hg. There was a statistically significant decrease ($p<0.001$) in both systolic blood pressure by 12 mm Hg and diastolic blood pressure by 5 mmHg after 4 weeks of APAP therapy. With four weeks of treatment with FPAP, there was a significant decrease in heart rate by 4.4 beats/min, indicating a reduction in sympathetic tone and a significant heart rate decrease was not seen in the APAP group. Thus, there was a statistical improvement in S.B.P and heart rate with four weeks of FPAP therapy and S.B.P and D.B.P with four weeks of APAP therapy.

In a study by Patruno et al[57], office B.P. was recorded at baseline and after 3 months of treatment with FPAP and APAP. OSA indexes were reduced in both groups following treatment. They observed a significant reduction in S.B.P (from 144 ± 10 to 132 ± 8 mm

Hg) and D.B.P (from 88 ± 4 to 79 ± 6 mm Hg) in the FPAP group but not in the APAP group (S.B.P, 142 ± 12 to 136 ± 6 mm Hg; D.B.P, 87.5 ± 4 to 86 ± 4 mm Hg). FPAP reduced B.P to a greater extent as compared to APAP. In a study by Pepin et al,[58] there was no significant reduction in office B.P as compared to baseline at the end of 4 months in both FPAP or APAP groups. Major limitations of the study were the lack of in-laboratory CPAP titration and poor patient compliance. The percentage of patients with OSA using CPAP more than 4 hr/night was 64.6% and 66.5% in the FPAP and APAP arms.

In the present study, there was no significant change in the Ewings battery of tests with FPAP therapy. Only two out of six components of the Ewings battery of tests (S.B.P. response to active standing from supine position and D.B.P. response to active standing from supine position), showed statistically significant improvement with 4 weeks of APAP therapy. Thus, a significant reduction in S.B.P, D.B.P along with improvement in blood pressure response to standing, which reflects the normalization of baroreflex sensitivity and reduction in orthostatic hypotension, suggests that APAP helps in reducing hypertension and improvement in cardiac autonomic function.

In a study by Veale D et al[55] in six OSA patients, therapy autonomic functions assessed by Ewings battery of tests improved after one year of CPAP. In another study on obese OSA patients with two months of CPAP heart rate response to the deep breath test and systemic blood pressure response to the handgrip test were improved, thus associated with reduced sympathetic activity[54].

Comparison of AHI, Daytime Sleepiness, Fatigue and Sleep Quality of Life

In our study, the mean ESS score reduced in both the FPAP and APAP groups after 1 month of treatment. It was lower after FPAP use when compared with APAP. However, the difference between the two was not statistically significant. This has also been noted in other studies, where no difference has been found in ESS scores between FPAP and APAP. In a study where there was a significant difference in the ESS score between FPAP and APAP with a greater reduction observed with APAP; the difference was only 0.6 between the ESS of the two groups. Moreover, the objective sleepiness measures used to compare the groups did not show any significant difference between the two groups in the study.[80] Similar trends were noted in FSS and PSQI scores. Both decreased more with FPAP as compared to APAP. However, the difference was only marginal and not statistically significant. This was the first study comparing the fatigue and sleep quality scores between the two PAP modalities. Overall, the above findings suggest that both FPAP and APAP are equally effective in terms of improvement in daytime sleepiness, fatigue and sleep quality of life.

Comparison of FPAP and APAP pressures

In our study, we found that there was a significant difference between mean FPAP pressures achieved by in laboratory manual titration when compared with 95th percentile APAP pressures from the device. The manually titrated pressures were higher as compared to APAP pressures by about 2 cm of H2O. Ayas et al. conducted a meta-analysis encompassing all available randomized trials comparing APAP with FPAP. The analysis included nine studies involving 282 patients. They compared the mean APAP pressures with the FPAP pressures and concluded that the mean applied pressure of APAP

was around 2.2 cm of H2O less than that of FPAP[81]. Various other studies have failed to show significant differences in the manually titrated CPAP pressures and APAP pressures[82,83].

There was a lack of significant changes in overall heart rate variability and other autonomic functions with both FPAP and APAP, which signifies that not all components of cardiac autonomic functions improve with short-term APAP therapy.

Given PAP therapy is primarily targeted towards improving breathing during sleep and reducing apnea-hypopnea index, improving quality of sleep, daytime wakefulness, and improved cognitive function, its effects on HRV after a shorter duration are subtle and might require a longer duration of therapy to manifest.

Thus, we found that although there was a significant decrease in office S.B.P in both FPAP and APAP and D.B.P in FPAP and improvement in HRV in FPAP. There was no significant difference in other sympathetic parameters. This could be explained by

1. Probably, short-term interventions may not be sufficient to produce significant changes in cardiac autonomic activity in populations with long-standing autonomic imbalances such as patients with OSA. Although nocturnal autonomic changes might improve with both FPAP and APAP, daytime autonomic changes difference might take some more time to improve.
2. As office B.P. got better in most of the patients and autonomic changes did not change as expected: probably there are other pathways (like renin angiotensinogen system) apart from autonomic function that regulate B.P. control in OSA patients.

SUMMARY

OSA is associated with hypopnea and apnea due to repetitive episodes of partial or complete closure of upper airways, which leads to changes in intrathoracic pressure, sleep fragmentation, surge in sympathetic activity and changes in heart rate regulation. The extent of cardiovascular variability is linked to the severity of OSA. CPAP is the first-line therapy of OSA patients with proven efficacy and safety. APAP is another treatment option in OSA patients, delivering variable airway pressure adjusting according to the AHI. Data comparing CPAP and APAP cardiac autonomic functions indicating cardiovascular health are limited. The present study is undertaken to compare both fixed CPAP and APAP therapies in the treatment of OSA and their efficacy in the improvement of cardiac autonomic activities in OSA patients.

Thirty-six patients underwent baseline HRV and Ewing's battery of Autonomic function test, followed by a cross-over study of fixed PAP and automatic PAP for four weeks in each arm with a washout of two weeks between both arms. Along with HRV and Ewing's battery of Autonomic function tests, ESS, FSS and PSQI scores were also evaluated at baseline and after each arm. The PAP questionnaire was assessed after both the PAP therapy.

Key findings:

- With four weeks of FPAP and APAP, there was a slight increase in total HRV, HFnu and a minimal reduction in LFnu and LF/HF ratio, which suggests that there is improvement in autonomic dysfunction with both the PAP therapies.

- There was no statistical difference in frequency domain parameters of HRV with both FPAP and APAP.
- Among the time domain parameters assessed, RMSSD showed a statistically significant increase after 4 weeks of FPAP, showing improvement in parasympathetic nervous system activity. Though RMSSD after APAP and pNN50 with both FPAP and APAP did not increase significantly, results are in favour of improvement in the parasympathetic component and balance in the autonomic nervous system with both the PAP therapies.
- With FPAP, there was a statistically significant reduction in S.B.P and H.R. and in S.B.P and D.B.P with APAP.
- There were no significant changes in Ewings battery of tests with FPAP.
- With APAP, only two out of six components of the Ewings battery of tests, S.B.P.'s response to active standing from a supine position and D.B.P.'s response to active standing from the supine position showed statistically significant improvement.
- There was a decrease in sleepiness and fatigue and improved quality of sleep in both arms, but there was no difference between both modalities.
- No difference was present in patient preference for either PAP therapy.
- The pressure achieved through manual laboratory titration was significantly higher when compared with the 95^{th} percentile pressure of 4 weeks of APAP use.

STRENGTHS AND LIMITATIONS OF THE STUDY

STRENGTHS:

- It was a randomised cross-over trial with each participant receiving both treatments, thus eliminating selection bias, the effect of confounding variables and inter-subject differences.
- Our study involved the prescription of FPAP based on in-lab attended manual PAP titration. Very few studies have used manual titration to compare the effects between FPAP and APAP.
- The present study included patients who had adequate compliance with both FPAP and APAP therapy. This eliminates the potential bias arising from inconsistent usage of the treatments, thereby ensuring the validity of the comparative analysis between the two groups.
- HRV measurement and Ewings battery of tests were performed in the morning between 9.00 A.M. to 12 P.M. to avoid diurnal variations in the analysis.

LIMITATIONS:

- The sample size in our study was small. A small sample size increases the likelihood of type-II errors, where the potentially significant effects are missed. This explains why HRV parameters, though showing improvement, were not statistically significant.
- We observed the effects of the 1-month treatment of FPAP and APAP. A shorter duration of intervention for four weeks may not be enough to observe sustained long-term effects.

- HRV can vary between patients due to factors like age, gender, stress levels, medication use, and lifestyle, leading to wide confidence intervals.

CONCLUSION

OSA patients are at increased risk of cardiovascular complications due to high levels of sympathetic drive. Treatment with both FPAP and APAP results in milder improvement in cardiac autonomic functions by reducing sympathetic activity and improving parasympathetic activity. The change was not statistically significant to assess the long-term benefits of cardiac sympathetic and parasympathetic imbalance with PAP therapy. More studies for longer duration are required to study the long-term effects of both CPAP and APAP in improvement in cardiac autonomic function tests.

REFERENCES

1. Lee W, Nagubadi S, Kryger MH, Mokhlesi B. Epidemiology of obstructive sleep apnea: A population-based perspective. Expert Rev Respir Med 2008;2:349-64.
2. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230-5.
3. Goyal A, Pakhare A, Joshi A. Prevalence of OSA in Indian population and diagnostic accuracy of different tools for OSA. ERJ Open Research [Internet]. 2023 Apr 20 [cited 2024 Apr 30];9(suppl 11).
4. Sharma SK, Kumpawat S, Banga A, Goel A. Prevalence and risk factors of obstructive sleep apnea syndrome in a population of Delhi, India. Chest. 2006 Jul 1;130(1):149-56.
5. Guzik P, Piskorski J, Awan K, Krauze T, Fitzpatrick M, Baranchuk A. Obstructive sleep apnea and heart rate asymmetry microstructure during sleep. Clinical Autonomic Research. 2013 Apr;23(2):91-100.
6. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. The Lancet. 2009 Jan 3;373(9657):82-93.
7. Somers, V.K., Dyken, M.E., Mark, A.L. & Abboud, F.M. 1993. Sympathetic nerve activity during sleep in normal humans. N Engl J Med 328, 303–307.
8. Somers, V.K., Dyken, M.E., Clary, M.P. & Abboud, F.M. 1995. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 96, 1897–1904.
9. May AM, Van Wagoner DR, Mehra R. Obstructive sleep apnea and cardiac arrhythmogenesis: mechanistic insights. Chest. 2017;151:225–241. doi: 10.1016/j.chest.2016.09.014.

10. Narkiewicz, K., Montano, N., Cogliati, C., de Borne, P.J.H., Dyken, M.E. & Somers, V.K. 1998. Altered cardiovascular variability in obstructive sleep apnea. Circulation 98, 1071– 1077.
11. Phillips, B.G., Narkiewicz, K., Pesek, C.A., Haynes, W.G., Dyken, M.E. & Somers, V.K. 1999. Effects of obstructivesleep apnea on endothelin-1 and blood pressure. J Hypertens 17, 61–66.
12. Kato, M., Roberts-Thomson, P., Phillips, B.G. et al. 2000. Impairment of endothelium-dependent vasodilation ofresistance vessels in patients with obstructive sleep apnea. Circulation 102, 2607–2610.
13. Frattola, A., Parati, G., Cuspidi, C., Albini, F. & Mancia, G. 1993. Prognostic value of 24-hour blood pressure variability. J Hypertens 11, 1133–1137.
14. Saul, J.P., Arai, Y., Berger, R.D., Lilly, L.S., Colucci, W.S. & Cohen, R.J. 1988. Assessment of autonomic regulation in chronic congestive heart failure by spectral analysis. Am J Cardiol 61, 1292–1299.
15. Kleiger, R.E., Miller, J.P., Bigger, J.T. & Moss, A.J. 1987. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 59, 256–262.
16. Cortelli P, Parchi P, Sforza E, Contin M, Pierangeli G, Barletta G, et al. Cardiovascular autonomic dysfunction in normotensive awake subjects with obstructive sleep apnoea syndrome. Clin Auton Res. 1994 Apr 1;4(1):57–62.
17. Parati G, Di Rienzo M, Bonsignore MR, Insalaco G, Marrone O, Castiglioni P, et al. Autonomic cardiac regulation in obstructive sleep apnea syndrome: evidence from

spontaneous baroreflex analysis during sleep. J Hypertens. 1997 Dec;15(12 Pt 2):1621–6.

18. Tamisier R, Lévy P, Pépin JL. Do patients with obstructive sleep apnoea deserve new dedicated antihypertensive strategies? Thorax 2017;72:495–7.
19. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. Medical and biological engineering and computing. 2006 Dec;44(12):1031-51.
20. Mark BL, Lightfoot JT. Reproducibility of resting heart rate variability with short sampling periods. Can J Appl Physiol 1999; 24: 337-48.
21. Limphanudom P, Chierakul N, Pinyopattarakul N, Nana A, Naruman C, Tangchityongsiva S, Wattanapa WB, Jenwitheesak A. Recovery of heart rate variability in patients with moderate to severe obstructive sleep apnea after 6-month continuous positive airway pressure treatment. JOURNAL-MEDICAL ASSOCIATION OF THAILAND. 2007 Aug 1;90(8):1530.
22. Karemaker JM. Counterpoint: respiratory sinus arrhythmia is due to the baroreflex mechanism. Journal of applied physiology. 2009 May;106(5):1742-3.
23. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Frontiers in public health. 2017:258.
24. Wiklund U, Olofsson BO, Franklin K, Blom H, Bjerle P, Niklasson U. Autonomic cardiovascular regulation in patients with obstructive sleep apnoea: a study based on spectral analysis of heart rate variability. Clinical physiology (Oxford, England). 2000 May 1;20(3):234-41.

25. Reynolds EB, Seda G, Ware JC, Vinik AI, Risk MR, Fishback NF. Autonomic function in sleep apnea patients: increased heart rate variability except during REM sleep in obese patients. Sleep and Breathing. 2007 Mar;11(1):53-60.
26. Park DH, Shin CJ, Hong SC, Yu J, Ryu SH, Kim EJ, Shin HB, Shin BH. Correlation between the severity of obstructive sleep apnea and heart rate variability indices. Journal of Korean medical science. 2008 Apr 1;23(2):226-31.
27. Torre-Bouscoulet L, Meza-Vargas MS, Castorena-Maldonado A, Reyes-Zúñiga M, Pérez-Padilla R. Autoadjusting Positive Pressure Trial in Adults with Sleep Apnea Assessed by a Simplified Diagnostic Approach. J Clin Sleep Med. 2008 Aug 15;4(4):341–7.
28. National Institute for Health and Clinical Excellence. Continuous positive airway pressure for obstructive sleep apnoea/hypopnoea syndrome. Available online: https://www.nice.org.uk/guidance/ta139/resources/continuous-positive-airway-pressure-for-obstructive-sleep-apnoeahypopnoea-syndrome-374791501. Last accessed on 15th August 2019.
29. Sullivan C, Berthon-Jones M, Issa F, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. The Lancet. 1981 Apr 18;317(8225):862-5.
30. Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, Lavie L, Pépin JL. Obstructive sleep apnoea syndrome. Nature reviews Disease primers. 2015 Jun 25;1(1):1-21.
31. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG. Sleep apnea and cardiovascular disease: An

American heart association/American college of cardiology foundation scientific statement from the American heart association council for high blood pressure research professional education committee, council on clinical cardiology, stroke council, and council on cardiovascular nursing in collaboration with the national heart, lung, and blood institute national center on sleep disorders research (national institutes of health). Journal of the American College of Cardiology. 2008 Aug 19;52(8):686-717.

32. Narkiewicz K, Kato M, Phillips BG, Pesek CA, Davison DE, Somers VK. Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. Circulation. 1999 Dec 7;100(23):2332-5.
33. Hedner J, Darpo B, Ejnell H, Carlson J, Caidahl K. Reduction in sympathetic activity after long-term CPAP treatment in sleep apnoea: cardiovascular implications. European Respiratory Journal. 1995 Feb 1;8(2):222-9.
34. Maser RE, Lenhard MJ, Rizzo AA, Vasile AA. Continuous positive airway pressure therapy improves cardiovascular autonomic function for persons with sleep-disordered breathing. Chest. 2008 Jan 1;133(1):86-91.
35. Ip S, D'Ambrosio C, Patel K, Obadan N, Kitsios GD, Chung M, Balk EM. Auto-titrating versus fixed continuous positive airway pressure for the treatment of obstructive sleep apnea: a systematic review with meta-analyses. Systematic reviews. 2012 Dec;1(1):1-24.
36. Najib T. Ayas, MD, MPH, Sanjay R. Patel, MD, Atul Malhotra, MD, Michael Schulzer, MD, PhD, Mark Malhotra, David Jung, John Fleetham, MD, David P. White, MD, Auto- Titrating Versus Standard Continuous Positive Airway Pressure for

the Treatment of Obstructive Sleep Apnea: Results of a Meta-analysis, Sleep, Volume 27, Issue 2, March 2004, Pages 249–253.

37. Boudewyns A, Van de Heyning P, De Backer W. Appearance of central apnoea in a patient treated by auto-CPAP for obstructive sleep apnoea. Respir Med. 1998;92(6):891-893.
38. Patruno V, Tobaldini E, Bianchi AM, Mendez MO, Coletti O, Costantino G, Montano N. Acute effects of autoadjusting and fixed continuous positive airway pressure treatments on cardiorespiratory coupling in obese patients with obstructive sleep apnea. European journal of internal medicine. 2014 Feb 1;25(2):164-8.
39. Patruno V, Aiolfi S, Constantino G, Murgia R, Selmi C, Malliani A, et al. Fixed and autoadjusting continuous positive airway pressure treatments are not similar in reducing cardiovascular risk factors in patients with obstructive sleep apnea. Chest. 2007;131(5):1393- 1399.
40. Fuchs FS, Wiest GH, Frank M, Harsch IA, Schahin SP, Hahn EG, Ficker JH. Auto-CPAP therapy for obstructive sleep apnea: induction of microarousals by automatic variations of CPAP pressure?. Sleep. 2002 Aug 1;25(5):512-6.
41. Sangal RB, Sudan N. Baseline lighter sleep and lower saturation are associated with improved sleepiness and adherence on continuous rather than autotitrating positive airway pressure. Clinical EEG and Neuroscience. 2020 May;51(3):174-9.
42. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med. 2019 Aug;7(8):687–98.

43. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med. 2019 Aug;7(8):687–98.
44. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC,et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep Med Rev. 2017;34:70-81.
45. Narkiewicz K., van de Borne P.J., Montano N., Dyken M.E., Phillips B.G., Somers V.K. Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. Circulation. 1998;97:943–945. doi: 10.1161/01.CIR.97.10.943.
46. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet. 1981;1:862–5.
47. Patel SR, White DP, Malhotra A, Stanchina ML, Ayas NT. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: Results of a meta-analysis. Arch Intern Med. 2003;163:565–71.
48. Gay P, Weaver T, Loube D, Iber C, Positive Airway Pressure Task Force, Standards of Practice Committee, et al. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. Sleep. 2006 Mar;29(3):381–401.
49. Berry RB, Parish JM, Hartse KM. The use of auto-titrating continuous positive airway pressure for treatment of adult obstructive sleep apnea. An American Academy of Sleep Medicine review. Sleep. 2002 Mar 15;25(2):148–73.

50. Ayas NT, Patel SR, Malhotra A, Schulzer M, Malhotra M, Jung D, Fleetham J, White DP. Auto-titrating versus standard continuous positive airway pressure for the treatment of obstructive sleep apnea: results of a meta-analysis. Sleep. 2004 Mar 15;27(2):249-53. doi: 10.1093/sleep/27.2.249. PMID: 15124718.
51. Karasulu L, Epöztürk PÖ, Sökücü SN, Dalar L, Altın S. Improving heart rate variability in sleep apnea patients: differences in treatment with auto-titrating positive airway pressure (APAP) versus conventional CPAP. Lung. 2010 Aug;188(4):315-20.
52. Kufoy E, Palma JA, Lopez J, Alegre M, Urrestarazu E, Artieda J, Iriarte J. Changes in the heart rate variability in patients with obstructive sleep apnea and its response to acute CPAP treatment. PLoS One. 2012 Mar 16;7(3):e33769.
53. Palma JA, Iriarte J, Fernandez S, Alegre M, Valencia M, Artieda J, Urrestarazu E. Long-term continuous positive airway pressure therapy improves cardiac autonomic tone during sleep in patients with obstructive sleep apnea. Clinical Autonomic Research. 2015 Aug;25(4):225-32.
54. Quadri F, Boni E, Pini L, et al. Exercise tolerance in obstructive sleep apnea-hypopnea (OSAH), before and after CPAP treatment: Effects of autonomic dysfunction improvement. Respir Physiol Neurobiol. 2017;236:51-56.
55. Veale D, Pepin JL, Wuyam B, Levy PA. Abnormal autonomic stress responses in obstructive sleep apnoea are reversed by nasal continuous positive airway pressure. European Respiratory Journal. 1996 Oct 1;9(10):2122-6.
56. Treptow E, Pepin JL, Bailly S, et al. Reduction in sympathetic tone in patients with obstructive sleep apnoea: is fixed CPAP more effective than APAP? A randomised,

parallel trial protocol. BMJ Open 2019;9:e024253. doi:10.1136/ bmjopen-2018-024253.

57. Patruno V, Aiolfi S, Costantino G, Murgia R, Selmi C, Malliani A, Montano N. Fixed and autoadjusting continuous positive airway pressure treatments are not similar in reducing cardiovascular risk factors in patients with obstructive sleep apnea. Chest. 2007 May 1;131(5):1393-9.
58. Pépin JL, Tamisier R, Baguet JP, Lepaulle B, Arbib F, Arnol N, Timsit JF, Lévy P. Fixed-pressure CPAP versus auto-adjusting CPAP: comparison of efficacy on blood pressure in obstructive sleep apnoea, a randomised clinical trial. Thorax. 2016 Aug 1;71(8):726-33.
59. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc. 2008;5:173–8.
60. Alves A, Gigante AR, Machado D, Sanches I, Marçoa R, Franco I, et al. Transition from APAP to CPAP may be a cost-effective health intervention in OSA patients. J Bras Pneumol. 2021;47(6):e20210286.
61. Vennelle M, White S, Riha RL, Mackay TW, Engleman HM, Douglas NJ. Randomized Controlled Trial of Variable-Pressure Versus Fixed-Pressure Continuous Positive Airway Pressure (CPAP) Treatment for Patients with Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS). Sleep. 2010 Feb 1;33(2):267–71.
62. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. Journal of Clinical Sleep Medicine J Clin Sleep Med Journal of Clinical Sleep Medicine. 2017;1313:479-504.

63. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. J Clin Sleep Med. 2012;8:597–619.
64. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017;1313:479-504.
65. Kushida CA, Chediak A, Berry RB, Brown LK, Gozal D, Iber C, et al. Positive Airway Pressure Titration Task Force; American Academy of Sleep Medicine. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med. 2008;4:157-71.
66. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation. 1991;84:1482-1492.
67. Partinen M, Jamieson A, Guilleminault C. Long-term outcome for obstructive sleep apnea syndrome patients: mortality. Chest 1988;94:1200-4.
68. Somers VK, Dyken M, Clary M, et al. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995;96:1897-904.
69. Clark RW, Boudoulas H, Schaal SF, et al. Adrenergic hyperactivity and cardiac abnormality in primary disor- ders of sleep. Neurology 1980;30:113-9.
70. Song SO, He K, Narla RR, Kang HG, Ryu HU, Boyko EJ. Metabolic Consequences of Obstructive Sleep Apnea Especially Pertaining to Diabetes Mellitus and Insulin Sensitivity. Diabetes Metab J. 2019 Apr;43(2):144–55.

71. Waravdekar NV, Sinoway LI, Zwillich CW, et al. Influ- ence of treatment on muscle sympathetic nerve activity in sleep apnea. Am J Respir Crit Care Med 1996;153: 1333-8.

72. Roux F, D'Ambrosio C, Mohsenin V. Sleep-related breathing disorders and cardiovascular disease. Am J Med 2000;108:396-402.

73. Garrigue S, Bordier P, Jais P, et al. Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med 2002; 346(6):404-12.

74. Narkiewicz K, Somers VK. Sympathetic nerve activity in obstructive sleep apnoea. Acta Physiologica Scandinavica. 2003 Mar;177(3):385-90.

75. Narkiewicz K, Somers VK. Cardiovascular variability characteristics in obstructive sleep apnea. Autonomic Neuroscience. 2001 Jul 20;90(1-2):89-94.

76. Sharma SK, Katoch VM, Mohan A, Kadhiravan T, Elavarasi A, Ragesh R, et al. Consensus and evidence-based Indian initiative on obstructive sleep apnea guidelines 2014 (first edition). Lung India. 2015;32(4):422–34.

77. Nelesen RA, Yu H, Ziegle MG, Mill PJ, Clause JL, Dimsdale JE. Continuous positive airway pressure normalizes cardiac autonomic and hemodynamic responses to a laboratory stressor in apneic patients. Chest 2001; 119: 1092-101.

78. Milleron O, Pilli'ere R, Foucher A, Roquefeuil F, Aegerter P, Jondeau G. Benefits of obstructive sleep apnoea treatment in coronary artery disease: a long-term follow-up study. Eur Heart J 2004; 25:728–34.

79. Roche F, Court-Fortune I, Pichot V. Reduced cardiac sympathetic autonomic tone after long term nasal continuous positive pressure in obstruc- tive sleep apnea syndrome. Clin Physiol 1999; 2: 127-34.

80. Vennelle M, White S, Riha RL, Mackay TW, Engleman HM, Douglas NJ. Randomized Controlled Trial of Variable-Pressure Versus Fixed-Pressure Continuous Positive Airway Pressure (CPAP) Treatment for Patients with Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS). Sleep. 2010 Feb 1;33(2):267–71.
81. Ayas NT, Patel SR, Malhotra A, Schulzer M, Malhotra M, Jung D, et al. Auto-titrating versus standard continuous positive airway pressure for the treatment of obstructive sleep apnea: results of a meta-analysis. Sleep. 2004 Mar 15;27(2):249–53.
82. Masa JF, Jiménez A, Durán J, Capote F, Monasterio C, Mayos M, et al. Alternative methods of titrating continuous positive airway pressure: a large multicenter study. Am J Respir Crit Care Med. 2004 Dec 1;170(11):1218–24.
83. Kim H, Lee M, Hwangbo Y, Yang KI. Automatic Derivation of Continuous Positive Airway Pressure Settings: Comparison with In-Laboratory Titration. J Clin Neurol. 2020 Apr;16(2):314–20.

ANNEXURES

ANNEXURE I

PARTICIPANT INFORMED CONSENT FORM (PICF)

Participant identification number for this study:_____

Title of project: **Comparison of autonomic function changes by fixed pressure versus auto adjusting continuous positive airway pressure treatments in patients with Obstructive Sleep Apnea.**

Name of Student Investigator: **Dr S. Anusha Rao** Tel. No(s). 9494647350

Name of Thesis Guide: **Dr Abhishek Goyal**

The contents of the information sheet dated …….. that was provided have been read carefully by me / explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions. The nature and purpose of the study and its potential risks/benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected.

I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS. I give permission for these individuals to have access to my records.

I agree to take part in the above study.

---------- Date:
(Signatures / Left Thumb Impression) Place:

Name of the Participant: _____
Son / Daughter / Spouse of:_____
Complete postal address: _____
This is to certify that the above consent has been obtained in my presence.

Signatures of the Principal Investigator Date:
Place:

1) Witness – 1	2) Witness – 2
----------	----------
Signatures	Signatures
Name:	Name:
Address:	Address:

सहभागी सूचित सहमति प्रपत्र

इस जांच के लिये सहभागी का पहचान नंबर .....

अनुसंधान शीर्षक: ऑब्सट्रक्टिव स्लीप एपनिया के रोगियों में निरंतर सकारात्मक वायुमार्ग दबाव उपचार में निश्चित दबाव बनाम ऑटो समायोजन द्वारा स्वायत्त कार्य परिवर्तनों की तुलना

छात्र अन्वेषक का नाम: डॉ. अनुषा राव **फोन नं:** 9494647350

शोध मार्गदर्शक का नाम: डॉ. अभिषेक गोयल

मैंने दिनांक ..... के प्रतिभागी सूचना पत्र में दिये गए सभी तथ्यों को ध्यान पूर्वक पढ़ लिया है एवं मुझे समझ में आने वाली भाषा में विस्तारपूर्वक समझा दिया गया है और मैंने तथ्यों को भली भांति से समझ लिया है। मैं प्रमाणित करता/ करती हूँ,कि मुझे प्रश्न पूछने का पूर्ण अवसर दिया गया है । मुझे इस अध्ययन की प्रकृति एवं उद्देश्य और इसके संभावित लाभ एवं जोखिम और अध्ययन की संभावित अवधि अन्य प्रासंगिक जानकारी के बारे में विस्तार पूर्वक समझा दिया गया है। मैं समझता/ समझती हूँ कि इस अध्ययन में मेरी भागीदारी स्वेच्छिक है तथा मैं इस अध्ययन से किसी भी समय बिना कोई कारण बताए, बिना मेरी चिकित्सा देखभाल या कानूनी अधिकारों के प्रभावित हुए अपना नाम वापिस ले सकता / सकती हूँ।

मैं समझता/ समझती हूँ कि इस अनुसंधान में मेरी सहभागिता से मेरे बारे में एकत्र जानकारी और चिकित्सीय दस्तावेजों को एम्स अस्पताल के जिम्मेदार लोगों द्वारा देखा जायेगा। मैं इन व्यक्तियों को अपने रिकॉर्ड देखने कि अनुमति प्रदान करता/ करती हूँ। मैं उपर्युक्त अध्ययन में भाग लेने के लिए अपनी सहमति प्रदान करता / करती हूँ।

---------- ---------- ---------

सहभागी के हस्ताक्षर / बांए अंगूठे का निशान दिनांक स्थान

सहभागी का नाम: _____

पिता/ पति का नाम: _____

पूरा पता: _____

यह प्रमाणित किया जाता है कि उपर्युक्त सहमति मेरी उपस्थिति में ली गई हैं।

_____ _____ _____

छात्र अन्वेषक के हस्ताक्षर दिनांक स्थान

---------- ----------

1. गवाह के हस्ताक्षर

नाम: _____

पता: _____

2. गवाह के हस्ताक्षर

नाम: _____

पता: _____

ANNEXURE 2

PARTICIPANT INFORMATION SHEET

1. **STUDY TITLE:** Comparison of autonomic function changes by fixed pressure versus auto adjusting continuous positive airway pressure treatments in patients with Obstructive Sleep Apnea
2. **STUDY INVESTIGATORS:**
3. **Student:** Dr S. Anusha Rao, Senior Resident(Academic) Dept. of Pulmonary Medicine
4. **Guide:** Dr Abhishek Goyal, Additional Professor and HOD, Dept. of Pulmonary Medicine.
5. **Co- Guide/s:** Dr Alkesh Kumar Khurana, Associate Professor, Dept. of Pulmonary Medicine, Dr Ruchi Singh, Associate Professor, Dept. of Physiology.
6. **Introduction**:

   Obstructive sleep apnea (OSA) is associated with repetitive episodes of partial or complete closure of the upper airway which presents with excessive daytime sleepiness, loud snoring, observed episodes of breathing cessation during sleep, abrupt awakening from sleep accompanied by gasping or choking, difficulty concentrating during the day. It is associated with an increased risk of cardiovascular complications. PAP therapy has been shown to improve sleepiness, decrease the frequency of complications and improve the quality of life of OSA patients. We are conducting a research study to compare the efficacy of two different modes of PAP therapies-FPAP and APAP therapies, by measuring variations in heart rate (HRV) and Autonomic function tests(AFT) in moderate to severe OSA patients in AIIMS Bhopal. We would like to assess the improvement with regards to the symptoms, functional limitation and compliance to the treatment if you agree to take part voluntarily, we will ask you to sign a consent form.

7. **Purpose of the study:**

   Our study aims to measure and compare the parameters that determine the changes in Heart Rate and Autonomic Functions (by Ewing's battery of tests) with

reference to FPAP and APAP in newly diagnosed patients with moderate to severe OSA. This will help us find the subsets of patients who will benefit the most from fixed pressure CPAP therapy over Auto PAP or vice-versa.

8. Taking part – what it involves:

a. Do I have to take part?

Participation in this research is entirely voluntary. A decision to not take part, or to withdraw at any time, will not affect your rights or medical care in any way.

b. What is expected of me if I take part?

If you participate, you will undergo a split night study (Level I PSG) with manual CPAP titration polysomnography to determine the optimal pressures, after which, you will be randomly assigned to either FP CPAP or APAP therapy. After usage of the assigned therapy for 4 weeks, you will be switched to the other mode of PAP therapy for another four weeks. During the study period, you will be undergoing HRV testing and AFT at baseline and after each therapy. You are expected to be compliant with the assigned mode of PAP therapy throughout the study duration and visit us as per the scheduled follow-ups.

c. How long will my part in the study last?

Your participation in the study will last for ten weeks, during which you will be required to visit the hospital for 4 times. First, at the time of the split night sleep study and random assignment of first mode of PAP therapy. Then, at the end of 4^{th} week (4 weeks after the use of the initial mode of PAP therapy), then a week later at the end of 6^{th} week (allowing for two weeks of washout period and change to another mode of PAP therapy) and finally at the end of 10^{th} week (4 weeks after initiation of the second mode of PAP therapy) for protocol-based assessments of HRV, Ewing's battery of Autonomic function testing and ensuring adherence to PAP therapy.

d. Do I have to come for extra visits or undergo extra investigations for the study?

Extra visits and extra investigations are not required during the study.

e. What are the possible benefits of taking part?

Taking part in our study will not only help you to gain knowledge about the disease OSA which you are suffering from, but also in getting to know the type of CPAP device best suited to you for better management of your disease.

f. What are the possible disadvantages and risks of taking part?

There will not be any foreseeable disadvantages and risks because of the study. There will not be any risk of loss of your privacy and confidentiality of information collected and all possible measures will be taken to ensure safe data storage and access.

g. What happens to the information collected from me?

All information collected will be kept strictly confidential and not shared with anyone. Results from the study will be reported as group data and your identity will not be revealed in any way.

h. What if I change my mind regarding participation in the study?

You are entitled to change your mind and withdraw at any point time during the study without any disadvantage or penalty.

i. Whom do I contact for more information or if I have further questions or concerns?

If you want any information or have questions or concerns, you can contact:

Dr. S. Anusha Rao
Senior Resident (Academic),
Department of Pulmonology, AIIMS,
Bhopal
9494647350
anusharao116@gmail.com

Dr. Shashank Purwar
Member Secretary,
Institute Ethics Committee – Student Research
(7773010099, ihecpgr@aiimsbhopal.edu.in)

प्रतिभागी सूचना पत्रक

अध्ययन का शीर्षक: ऑब्सट्रक्टिव स्लीप एपनिया वाले रोगियों में निरंतर सकारात्मक वायुमार्ग दबाव उपचार को समायोजित करने वाले ऑटो समायोजन द्वारा स्वायत्त फ़ंक्शन परिवर्तनों की तुलना

अध्ययन जांचकर्ता:

छात्र: डॉ. एस. अनुषा राव, सीनियर रेजिडेंट (अकादमिक) पल्मोनरी मेडिसिन विभाग

मार्गदर्शक(गाइड): डॉ. अभिषेक गोयल, एडिशनल प्रोफेसर और एचओडी, पल्मोनरी मेडिसिन विभाग।

सह-मार्गदर्शिकाएँ: डॉ. अलकेश कुमार खुराना, एसोसिएट प्रोफेसर, पल्मोनरी मेडिसिन विभाग, डॉ. रुचि सिंह, एसोसिएट प्रोफेसर, फिजियोलॉजी विभाग।

परिचय:

ऑब्सट्रक्टिव स्लीप एपनिया (OSA) ऊपरी वायुमार्ग के आंशिक या पूर्ण बंद होने के दोहराए जाने वाले एपिसोड से जुड़ा हुआ है जो दिन की नींद, एलओड खर्राटे, नींद के दौरान सांस लेने की समाप्ति के ओ परोसा एपिसोड, हांफने या घुट के साथ नींद से जागने वाला एक ब्रुप्त जागृति, दिन के दौरान ध्यान केंद्रित करने के साथ प्रस्तुत करता है यह कार्डियोवैस्कुलर जटिलताओं के बढ़ते जोखिम से जुड़ा हुआ है। पीएपी थेरेपी को नींद में सुधार, जटिलताओं की आवृत्ति को कम करने और ओएसए रोगियों के जीवन की गुणवत्ता में सुधार करने के लिए दिखाया गया है। हम AIIMS भोपाल में मध्यम से गंभीर OSA रोगियों में हृदय गति (HRV) और स्वायत्त कार्य परीक्षणों (AFT) में भिन्नता को मापकर पीएपी थेरेपी के दो अलग-अलग तरीकों-फिक्स्ड प्रेशर सीपीएपी और ऑटो PAP थेरेपी की प्रभावकारिता की तुलना करने के लिए एक शोध अध्ययन कर रहे हैं। हम लक्षणों, कार्यात्मक सीमा और उपचार के अनुपालन के संबंध में सुधार का आकलन करना चाहते हैं यदि आप स्वेच्छा से भाग लेने के लिए सहमत हैं, तो हम आपको एक सहमति पत्र पर हस्ताक्षर करने के लिए कहेंगे।

अध्ययन का उद्देश्य:

हमारे अध्ययन का उद्देश्य मध्यम से गंभीर OSA वाले नए निदान रोगियों में निश्चित दबाव CPAP और APAP के संदर्भ में हृदय गति और स्वायत्त कार्यों (इविंग के परीक्षणों की बैटरी द्वारा) में परिवर्तन को निर्धारित करने वाले मापदंडों को मापना और तुलना

करना है। यह हमें उन रोगियों के सबसेट को खोजने में मदद करेगा जो ऑटो PAP या इसके विपरीत निश्चित दबाव CPAP थेरेपी से सबसे अधिक लाभान्वित होंगे।

भाग लेना - इसमें क्या शामिल है:
क्या मुझे भाग लेना चाहिए?
इस शोध में भागीदारी पूरी तरह से स्वैच्छिक है। भाग नहीं लेने, या किसी भी समय वापस लेने का निर्णय, किसी भी तरह से आपके अधिकारों या चिकित्सा देखभाल को प्रभावित नहीं करेगा।
अगर मैं भाग लेता हूं तो मुझसे क्या उम्मीद है?
यदि आप भाग लेते हैं, तो आप इष्टतम दबाव निर्धारित करने के लिए मैनुअल CPAP अनुमापन पॉलीसोम्नोग्राफी के साथ विभाजित रात के अध्ययन (स्तर I PSG) से गुजरेंगे, जिसके बाद, आपको यादृच्छिक रूप से FP CPAP या APAP थेरेपी को सौंपा जाएगा। 4 सप्ताह के लिए असाइन की गई चिकित्सा के उपयोग के बाद, आपको एक और 4 सप्ताह के लिए PAP थेरेपी के अन्य मोड में स्विच किया जाएगा। अध्ययन अवधि के दौरान, आप असाइन किए गए थेरेपी के प्रत्येक मोड से पहले और बाद में HRV परीक्षण और AFT से गुजरेंगे, जो कुल मिलाकर 4 यात्राएं हैं। आपको अध्ययन अवधि के दौरान PAP थेरेपी के असाइन किए गए मोड के अनुरूप होने की उम्मीद है और निर्धारित अनुवर्ती के अनुसार हमसे मिलने की उम्मीद है।
अध्ययन में मेरा हिस्सा कब तक चलेगा?

अध्ययन में आपकी भागीदारी दस सप्ताह तक चलेगी, जिसके दौरान आपको 4 बार अस्पताल जाना होगा। सबसे पहले, स्प्लिट नाइट स्लीप अध्ययन और पीएपी थेरेपी के पहले मोड के यादृच्छिक असाइनमेंट के समय। फिर, चौथे सप्ताह के अंत में (पीएपी थेरेपी के प्रारंभिक मोड के उपयोग के 4 सप्ताह बाद), फिर एक सप्ताह बाद छठे सप्ताह के अंत में (दो सप्ताह की वाशआउट अवधि और पीएपी थेरेपी के दूसरे तरीके में बदलाव की अनुमति) और अंत में 10वें सप्ताह के अंत में (पीएपी थेरेपी के दूसरे तरीके की शुरुआत के 4 सप्ताह बाद) एचआरवी के प्रोटोकॉल-आधारित आकलन के लिए, इविंग की ऑटोनोमिक फ़ंक्शन परीक्षण की बैटरी और पीएपी थेरेपी का पालन सुनिश्चित करना।

क्या मुझे अतिरिक्त यात्राओं के लिए आना होगा या अध्ययन के लिए अतिरिक्त जांच से गुजरना होगा?

अध्ययन के दौरान अतिरिक्त यात्राओं और अतिरिक्त जांच की आवश्यकता नहीं है।

भाग लेने में संभावित लाभ क्या हैं?
हमारे अध्ययन में भाग लेने से न केवल आपको OSA रोग के बारे में ज्ञान प्राप्त करने में मदद मिलेगी, जिससे आप पीड़ित हैं, बल्कि यह जानने में भी मदद मिलेगी कि आपकी बीमारी के बेहतर प्रबंधन के लिए आपके लिए सबसे उपयुक्त CPAP डिवाइस का प्रकार क्या है।

भाग लेने के संभावित नुकसान और जोखिम क्या हैं?
अध्ययन के कारण कोई अनुमानित नुकसान और जोखिम नहीं होगा। आपकी गोपनीयता और एकत्र की गई जानकारी की गोपनीयता के नुकसान का कोई जोखिम नहीं होगा और सुरक्षित डेटा भंडारण और पहुंच सुनिश्चित करने के लिए सभी संभव उपाय किए जाएंगे।

मुझसे एकत्र की गई जानकारी का क्या होता है?
एकत्र की गई सभी जानकारी को पूरी तरह से गोपनीय रखा जाएगा और किसी के साथ साझा नहीं किया जाएगा। अध्ययन के परिणामों को समूह डेटा के रूप में रिपोर्ट किया जाएगा और आपकी पहचान किसी भी तरह से प्रकट नहीं होगी।

क्या होगा अगर मैं अध्ययन में भागीदारी के बारे में अपना मन बदल दूं?
आप बिना किसी नुकसान या दंड के अध्ययन के दौरान किसी भी समय अपना मन बदलने और वापस लेने के हकदार हैं।

अधिक जानकारी के लिए मैं किससे संपर्क करूं या यदि मेरे पास आगे के प्रश्न या चिंताएं हैं?
यदि आप कोई जानकारी चाहते हैं या प्रश्न या चिंताएं हैं, तो आप संपर्क कर सकते हैं:

डॉ. एस. अनुषा राव
वरिष्ठ निवासी (अकादमिक),
पल्मोनोलॉजी विभाग, AIIMS,
भोपाल
9494647350
anusharao116@gmail.com

डॉ. शशांक पुरवार
सदस्य सचिव,
संस्थान आचार समिति - छात्र अनुसंधान
(7773010099, ihecpgr@aiimsbhopal.edu.in)

ANNEXURE 3

PATIENT CASE SHEET

NAME:

AGE / GENDER:

ADDRESS:

PHONE NUMBER:

HOSPITAL ID:

PRESENTING COMPLAINTS

- Excessive daytime sleepiness
- Loud snoring
- Observed episodes of breathing cessation during sleep
- Abrupt awakening from sleep accompanied by gasping or choking
- Awakening with Dry mouth or Sore throat
- Difficulty concentrating during the day
- Experiencing mood changes such as depression and irritability/
- Night time sweating
- Nocturia
- Morning headache
- Any other…….

COMORBIDITIES:

ANTIHYPERTENSIVE MEDICATIONS:

DIAGNOSTIC PSG DATE AND REPORT

Parameters	Values
AHI (Apnea Hypopnea Index)	
REM AHI	
NREM AHI	
T90	
ODI (Oxygen Desaturation Index)	
Nadir Oxygen saturation	

TITRATION STUDY

CPAP therapy	
Titration pressure	
Level of titration (optimal/suboptimal/adequate)	
Date advised	
Date started using	
Positional therapy advised(Y/N)	
If yes, since when	
Type of mask	

Parameters	**BASELINE**	**After 4 weeks of initial PAP Therapy**	**AFTER WASHOUT PERIOD**	**After 4 weeks of other PAP Therapy**
		Therapy type: (FP-CPAP / Auto PAP)		**Therapy type: (FP-CPAP / Auto PAP)**
Total				
LF/HF Ratio				
LFnu				
HFnu				
RMSSD				
PNN50				
S.B.P				
D.B.P				
H.R.				
Heartrate response to active standing from supine position				
Heartrate response to Valsalva maneuver				
Heartrate response to slow deep breathing				

B.P. response to sustained handgrip				
B.P. response to active standing from supine position				

EPWORTH SLEEPINESS SCALE (ESS)

In the following situations, how likely are you to doze off or fall asleep, in contrast to just feeling tired? Use the following scale to choose the most appropriate number for each situation:

0 : would never doze or sleep

1 : slight chance of dozing or sleeping

2 : moderate chance of dozing or sleeping

3 : high chance of dozing or sleeping

This refers to your usual way of life in recent times. Even if you haven't done some of these things recently, try to work out how they would have affected you. You must answer each question as best as you can.

Situation	**Chance of dozing or sleeping**			
Sitting and reading	0	1	2	3
Watching TV				
Sitting inactive in a public place				
As a passenger in a car for an hour without a break				
Lying down to rest in the afternoon when circumstances permit				
Sitting and talking to someone				
Sitting quietly after lunch without alcohol				
In a car, when it stops for a few minutes in the traffic				
Total Epworth score				

FATIGUE SEVERITY SCALE (FSS)

Please circle the number between 1 and 7 which you feel best fits the following statements. This refers to your usual way of life within the last week. 1 indicates "strongly disagree" and 7 indicates "strongly agree."

Read and circle a number	**Strongly Disagree**	——————— ——————— ->					**Strongly Agree**
My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
Exercise brings on my fatigue.	1	2	3	4	5	6	7
I am easily fatigued.	1	2	3	4	5	6	7
Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
My fatigue prevents sustained physical functioning	1	2	3	4	5	6	7
Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
Fatigue is among my most disabling symptoms.	1	2	3	4	5	6	7
Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

PITTSBURGH SLEEP QUALITY INDEX (PSQI)

Name:_____ Date: _____

During the past month,

1. When have you usually gone to bed?
2. How long (in minutes) has it taken you to fall asleep each night?
3. What time have you usually gotten up in the morning?

4. How many hours of actual sleep did you get at night? (Maybe different than the number of hours spent in bed)

During the past month, how often have youhad trouble sleeping because you	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				
J. Other reason (s), please describe				
K. How often you have had trouble sleeping because of this				

5. During the past month, how would you rate your sleep quality overall?

   Very good_____

   Fairly good_____

   Fairly bad _____

   Very bad _____

6. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

   Not during the past month

   Less than once a week

Once or twice a week

Three or more times a week

7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

   Not during the past month

   Less than once a week

   Once or twice a week

   Three or more times a week

8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

   No problem at all

   Only a very slight problem

   Somewhat of a problem

   A very big problem

9. Do you have a bed partner or room mate?

   No bed partner or roommate

   Partner/roommate in other room

   Partner in same room, but not same bed

   Partner in same bed

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .	**Not during the past month**	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
a) Loud snoring				
b) Long pauses between breaths while asleep				
c) Legs twitching or jerking while you sleep				
d) Episodes of disorientation or confusion during sleep				
e) Other restlessness while you sleep; please describe				

Total Score

CPAP QUESTIONAIRE (AFTER FPAP)

How much difficulty did you have tolerating CPAP?

no difficulty some difficulty great difficulty

1 2 3 4 5 6 7 8 9 10

How uncomfortable was the mask?

not uncomfortable somewhat uncomfortable very uncomfortable

1 2 3 4 5 6 7 8 9 10

How uncomfortable was the CPAP pressure

not uncomfortable somewhat uncomfortable very uncomfortable

1 2 3 4 5 6 7 8 9 10

What is the likelihood of you wearing the equipment at night almost every night ?

very likely likely highly unlikely

1 2 3 4 5 6 7 8 9 10

How beneficial do you think CPAP is going to be for your health and sleep?

very beneficial somewhat beneficial not beneficial

1 2 3 4 5 6 7 8 9 10

What is your attitude towards CPAP therapy?

greatly like CPAP somewhat like CPAPintensely dislike CPAP

1 2 3 4 5 6 7 8 9 10

CPAP QUESTIONAIRE (AFTER APAP)

How much difficulty did you have tolerating CPAP?

no difficulty some difficulty great difficulty

1 2 3 4 5 6 7 8 9 10

How uncomfortable was the mask?

not uncomfortable somewhat uncomfortable very uncomfortable

1 2 3 4 5 6 7 8 9 10

How uncomfortable was the CPAP pressure

not uncomfortable somewhat uncomfortable very uncomfortable

1 2 3 4 5 6 7 8 9 10

What is the likelihood of you wearing the equipment at night almost every night ?

very likely likely highly unlikely

1 2 3 4 5 6 7 8 9 10

How beneficial do you think CPAP is going to be for your health and sleep?

very beneficial somewhat beneficial not beneficial

1 2 3 4 5 6 7 8 9 10

What is your attitude towards CPAP therapy?

greatly like CPAP somewhat like CPAP intensely dislike CPAP

1 2 3 4 5 6 7 8 9 10

COMPLIANCE AND ADHERENCE WITH DIFFERENT PAP TREATMENTS

Parameters	AFTER FPAP	AFTER APAP
% of days with device usage		
Hours per day		
% days used > 4hrs		
Usage adequate or not		
Mask leak		
Claustrophobic		
Pressure intolerance		
Dry mouth		
CPAP QUESTIONAIRE		

DAYTIME SLEEPINESS, FATIGUE AND SLEEP QUALITY

BETWEEN FPAP AND APAP

PARAMETER	BASELINE	AFTER FPAP	AFTER APAP
ESS			
FSS			
PSQI			

Letter for permission for use of ESS questionnaire English and Hindi version

SPECIAL TERMS No75290

These User License Agreement Special Terms (Special Terms) are issued between Mapi Research Trust ("MRT") and ANUSHA RAO (User).

These Special Terms are in addition to any and all previous Special Terms under the User License Agreement General Terms.

These Special Terms include the terms and conditions of the User License Agreement General Terms, which are hereby incorporated by this reference as though the same was set forth in its entirety and shall be effective as of the Special Terms Effective Date set forth herein.

All capitalized terms which are not defined herein shall have the same meanings as set forth in the User License Agreement General Terms.

These Special Terms, including all attachments and the User License Agreement General Terms, contain the entire understanding of the Parties with respect to the subject matter herein and supersedes all previous agreements and undertakings with respect thereto. If the terms and conditions of these Special Terms or any attachment conflict with the terms and conditions of the User License Agreement General Terms, the terms and conditions of the User License Agreement General Terms will control, unless these Special Terms specifically acknowledge the conflict and expressly states that the conflicting term or provision found in these Special Terms control for these Special Terms only. These Special Terms may be modified only by written agreement signed by the Parties.

1. User information

User name	ANUSHA RAO
Category of User	University
User address	AIIMS Campus road,, Saket Nagar, , Bhopal, 462026, Habib Ganj , India
User VAT number	
User email	anusharao116@gmail.com

User phone	+919494647350
Billing information	AIIMS Campus road,, Saket Nagar, , Bhopal, 462026, Habib Ganj , India

SPECIAL TERMS No 75290 - 12 Jul 2022

© Mapi Research Trust,2022. The unauthorized modification, reproduction and use of any portion of this document is prohibited.

2. General information

Effective Date	Date of acceptance of these Special Terms by the User : 12 Jul 2022
Expiration Date (Term)	Upon completion of the Stated Purpose
Name of User's contact in charge of the request	ANUSHA RAO

3. Identification of the COA

Name of the COA	ESS - Epworth Sleepiness Scale
Author	Johns MW
Copyright Holder	Johns Murray W.
Copyright notice	ESS © MW Johns 1990-1997. Used under License.

SPECIAL TERMS No 75290 - 12 Jul 2022

© Mapi Research Trust,2022. The unauthorized modification, reproduction and use of any portion of this document is prohibited.

Bibliographic reference	Johns MW. The clinical assessment of daytime sleepiness in patients with obstructive sleep apnea. In:Surgery for snoring and obstructive sleep apnea syndrome, ed. Fabiani M. Kugler publications, The Hague, 2003: 283-295

	Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the epworth sleepiness scale: failure of the MSLT as a gold standard. J Sleep Res. 2000 Mar;9(1):5-11 (PubMed abstract) Johns MW. Sleepiness in different situations measured by the Epworth Sleepiness Scale. Sleep. 1994 Dec;17(8):703-10 (PubMed abstract) Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. Chest. 1993 Jan;103(1):30-6 (PubMed abstract) Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep. 1992 Aug;15(4):376-81 (PubMed abstract) Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991 Dec;14(6):540-5 (PubMed abstract)
Module(s)/version(s) needed	ESS

4. Context of use of the COA

The User undertakes to use the COA solely in the context of the Stated Purpose as defined hereafter. 4.1 Stated Purpose

Clinical research

SPECIAL TERMS No 75290 - 12 Jul 2022

© Mapi Research Trust,2022. The unauthorized modification, reproduction and use of any portion of this document is prohibited.

Title	Comparison of autonomic function changes by fixed pressure versus auto adjusting continuous positive airway pressure in patients with Moderate to Severe

	Obstructive Sleep Apnea
Study/protocol reference	
Sponsor	NA
Disease or condition	Obstructive Sleep Apnea
Type of research	Other: RCT
COA used as primary end point	No
Number of enrolled patients/subjects	32
Number of estimated failed patients/subjects	3
Number of submissions of the COA for each enrolled patient/subject	
Planned Term*	Start: 07/2022 End: 01/2025
Mode of Administration*	Paper
If electronic administration, please indicate mode of data collection	
Use of IT Company (e-vendor)	No

4.2 Country and languages

MRT grants the License to use the COA on the following countries and in the languages indicated in the table below:

© Mapi Research Trust,2022. The unauthorized modification, reproduction and use of any portion of this document is prohibited.

Version/Module	Language	For use in the following country
ESS	English	India
ESS	Hindi	India

The User understands that the countries indicated above are provided for information purposes. The User may use the COA in other countries than the ones indicated above.

PERMISSION TO USE PSQI

RE: Sleep Measures Request Form (PSQI)

Inbox

Gasiorowski, Mary <GasiorowskiMJ@upmc.edu> to me

Sent on behalf of Carolyn Weber

Research use of the PSQI:

Dear S Anusha Rao,

Mon, 11 Jul, 20:07 (2 days ago)

Thank you for your interest in our PSQI instrument. I can give you permission to use the PSQI **only** in non-commercially funded research or education or the product or service you are testing is not a commercial product or is in development by a commercial entity. It cannot be used for patient care either. If your use does **not** fall under those conditions, you can use the survey according to the following provisions:

This copyright in this form is owned by the University of Pittsburgh and may be reprinted without charge only for non-commercial research and educational purposes. You may not make changes or modifications of this form without prior written permission from the University of Pittsburgh. If you would like to use this instrument for commercial purposes or for commercially sponsored research, please contact the Innovation Institute at the University of Pittsburgh at 412-383-7669 for licensing information.

REQUEST

Subject
request for PSQI

Description
Respected Sir, I, Dr Anusha Rao, am pursuing the course of Doctor of Medicine in Pulmonary, Critical care and sleep medicine from the All India Institute of Medical Sciences, Bhopal, India. The topic for my dissertation is Comparison of Cardiac Autonomic Function Test changes by Fixed Pressure vs Auto adjusting continuous positive airway pressure treatments in patients with Moderate and Severe Obstructive Sleep Apnea in theDepartment of Pulmonary Medicine, AIIMS Bhopal We will be doing a detailed follow up of all OSA patients and need your permission to use the PSQI(Hindi and English version) in the research questionnaire. It will be used solely for scientific research purposes and not for any commercial purpose. Kindly grant me permission to use the PSQI(Hindi version and English version) for my thesis. Thanks and regards Dr Anusha Rao Department of Pulmonary Medicine All India Institute of Medical Sciences Bhopal

Other recipients (CC)
Not specified

Instruments
PSQI - Pittsburgh Sl

Version names
PSQI

Other instrument
No

Specify other instruments
Not specified

Languages (Start typing country name then select language)
Hindi for India | English for India

Mode of administration
Paper administration

Printing and Shipping
No

INFORMATION

Number
2210061

Type of request
Questionnaire Distribution

Assigned to
Inna Mazur

Creation date
12 Jul 2022

Modification date
24 Aug 2022

Status
Closed Completed

PERMISSION TO USE FSS

Permission to use fatigue severity scale for thesis Inbox ×

Anusha Rao <anusharao116@gmail.com> 13 Jul 2022, 22:32 (17 hours ago)
to drbirinder06

Respected Sir,

I am Dr. S Anusha Rao, pursuing D.M(Doctor Of Medicine) in Pulmonary, Critical care and sleep medicine from All India Institute of Medical Sciences, Bhopal, India.
The topic of my dissertation is "Comparison of autonomic function changes by fixed pressure versus auto adjusting continuous positive airway pressure treatments in patients with Obstructive Sleep Apnea". We will be doing a detailed follow up of 32 OSA patients and will be needing your permission to use Fatigue Severity Scale for the research questionnaire. It will be used solely for scientific research purposes and not for any commercial purposes.

Kindly grant me permission to use FSS for my thesis.

Thank you and regards,
Dr S Anusha Rao,
Department of Pulmonary Medicine,
All India Institute of Medical Sciences,
Bhopal.

Birinder paul 03:59 (12 hours ago)
to me

Dear Dr Anushs Rao
Kindly use the FSS questionnaire for ur research.
Thanks

MASTER CHART - BASELINE

S.NO	GENDER	AGE	NC	WC	HC	BMI	ESS	AHI	SBP	DBP	HR	BASELINE HRV						BASELINE AFT					
																		POSTURAL TEST		ISOMETRIC EXERC	DEEP BREATHING TEST	VALSALVA MANOEUVR	POSTURAL TEST
												TOTAL	LF	HF	LF/HF	RMSSD	PNN50	SBP	DBP	DBP			
1	M	50	42	102	102	34.6	10	80	100	70	70	2873	34.97	62.52	0.559	46.97	31.44	20	10	40	1.16	1.26	0.95
2	M	32	43	112	109	32.44997	17	118	126	92	88	231.8	83.78	17.3	4.844	5.97	0	-16	-12	8	1.0625	1.642	1
3	M	42	41	116	124	42	12	74	170	100	86	831	76.97	23.39	3.291	14.85	0	-8	-2	10	1.27	1.23	1.05
4	M	47	38	95	100	24.4	9	72	158	90	101	253.4	27.51	72.51	0.349	10.48	0.3591	-6	-8	10	1.15	1.5	1.06
5	M	62	42	93	96	25.80919	10	102	138	86	88	54.79	41.26	57.64	0.7159	9.857	0.1605	-12	-6	4	1.21	1.35	1.0625
6	F	51	32	105	92	27.23922	13	87	128	80	78	417.7	52.14	48.08	1.084	13.23	0	-2	-10	0	1.37	1.42	1.062
7	F	61	34	97	104	31.54375	17	61	140	80	64	572.5	64.17	36.39	1.763	22.61	2.66	-20	-6	2	1.308	1.375	1.05
8	M	38	40	109	111	35.5665	2	36	140	90	90	137.5	52.62	50.51	1.042	4.792	0	-12	-8	10	1.25	1.33	1.066
9	M	56	39	100	101	27.43484	11	67	130	98	80	86.02	64.81	38.84	1.669	4.854	0	-10	-14	6	1.23	1.28	1.06
10	M	47	41	104	108	29.41076	8	105	120	90	72	5395	59.08	42.37	1.394	30.63	11.25	10	6	20	1.39	1.94	1.105
11	M	50	40	105	102	29.41073	8	103	156	110	64	4779	59.55	40.86	1.458	37.43	12.93	-40	0	0	1.126	1.21	1.045
12	F	62	33	108	104	32.85668	14	53.7	152	100	70	715.1	45.86	53.55	0.856	16.75	0.479	0	0	2	1.13	1.25	1.05
13	F	70	33	102	98	30.22222	24	55	120	80	70	103.3	51.68	47.43	1.09	5.805	0	10	10	10	1.157	1.25	1.05
14	M	37	38	92	99	26.17519	4	58	136	90	80	796.8	49.14	48.39	1.015	21.41	1.872	-6	-10	6	1.186	1.26	1.04
15	M	63	40	90	94	26.1012	13	104	148	98	76	242	42.92	55.89	0.768	10.41	0.216	-8	-8	-4	1.12	1.22	1
16	M	42	36	96	96	28.67263	13	22	140	94	70	210.4	64.75	35.37	1.83	16.23	1.306	6	4	14	1.23	1.69	1.066
17	F	56	36	96	100	29.67495	13	24	124	82	72	231.7	76.47	23.22	3.294	9.738	0	-4	-4	4	1.25	1.43	1.052
18	M	65	43	105	95	29.4	8	37	130	90	78	366.6	84.14	17.23	4.884	5.212	0	2	-2	4	1.312	1.285	1
19	F	50	37	108	119	32.88889	12	33	148	78	74	4796	79.23	21.04	3.766	47.95	26.82	-26	-2	26	1.21	1.75	1.15
20	F	40	43	108	107	30.82483	24	116	158	102	88	1561	80.23	22.7	3.534	21.06	4.545	-2	-4	2	1.08	1.23	1.055
21	M	41	40	98	102	24.6755	8	51	158	104	70	675.2	69.51	30.1	2.31	17.88	0.849	-4	0	10	1.15	1.2	1
22	M	35	38	113	105	29.76084	9	35	156	122	86	594.9	72.12	28.09	2.567	16.58	0.478	-18	-4	20	1.163	2.07	1
23	F	55	36	113	108	31.11111	20	67	158	88	82	2794	60.82	36.76	1.654	52.52	1.408	-10	4	6	1.075	1.437	1
24	M	52	41	105	107	31.64432	18	99	162	96	77	698.7	69.42	30.41	2.28	12.91	0	-8	0	16	1.17	1.43	1
25	M	41	43	124	110	35.08303	16	92	176	116	85	473.2	87.86	10.46	8.4	11.58	0	-26	-2	4	1.12	1.25	1
26	F	43	32	94	100	29.93759	12	22	160	98	70	1278	42.79	55.97	0.764	20.73	0	0	2	8	1.18	1.25	1.05
27	F	35	43	118	108	32.24206	15	95	112	60	98	600.8	55.38	44.48	1.245	11.95	0	4	6	10	1.26	1.76	0.89
28	F	65	33	86	101	24.74745	1	34	132	88	79	532.8	74.08	22.52	3.29	21.82	3.044	-2	2	12	1	1.312	1.166
29	M	46	41	109	112	30.1194	2	69	130	100	77	231.6	21.54	77.1	0.279	16.1	0	0	0	2	1.14	1.312	1
30	M	46	35	100	102	25	13	32	146	96	82	3101	37.61	47.15	0.797	29.32	2.61	0	12	20	1.38	2.18	1.06
31	M	38	41	98	108	28.40816	24	130	140	90	70	5198	50.85	49.57	1.026	44.26	22.39	-6	-10	20	1.23	1.47	1.047
32	M	53	42	101	106	30.04	14	102	144	94	76	2794	29.3	64.9	0.45	15.22	0	6	2	20	1.13	1.33	0.94
33	M	28	41	90	97	27.63	12	16	164	112	90	231.6	68.19	33.82	2.016	12.85	0.197	6	2	8	1.44	1.5	0.94
34	M	60	44	102	103	27.68166	18	34	150	90	74	383.3	50.95	49.96	1.02	10.06	0	-10	0	0	1.057	1.69	1.062
35	M	60	40	111	112	32.33091	16	27	130	78	76	223.6	44.95	54.26	0.828	6.741	0	-10	-8	10	1.09	1.2	1.047
36	F	51	32	105	103	27.23922	13	87	144	82	66	417.7	75.68	25.61	2.955	26.91	4.61	-20	-4	-8	1.323	1.8	1.05

MASTER CHART

S.NO	BASELINE HRV and AFT																INITIAL PAP USED	HRV and AFT AFTER FIRST PAP THERAPY																AFT TOTAL	SECOND PAP THERAPY USED	HRV and AFT AFTER SECOND PAP									
	SBP	DBP	HR	TOTAL	LF	HF	LF/HF	RMSSD	PNN50	POSTURAL TEST SBP	DBP	ISOMETRIC DBP	DEEP BREATHING TEST	VALSALVA MANOEUVR	POSTURAL TEST	AFT TOTAL		SBP	DBP	HR	TOTAL	LF	HF	LF/HF	RMSSD	PNN50	POSTURAL SBP	DBP	ISOMETRIC DBP	DEEP BREATHING TEST	VALSALVA MANOEUVR	POSTURAL TEST	AFT TOTAL		SBP	DBP	HR	TOTAL	LF	HF	LF/HF	RMSSD	PNN50	POSTURAL TEST SBP
1	126	92	88	231.8	83.78	17.3	4.844	5.97	0	-16	-12	8	1.0625	1.642	1	2	BIPAP	120	80	78	799.2	65.21	33.1	1.972	21.65	0.67	-8	-2	4	1.15	1.6	1	2	AUTO	110	90	76	1322	73.17	27.1	2.7	15.49	0	2
2	170	100	86	831	76.97	23.39	3.291	14.85	0	-8	-2	10	1.27	1.23	1.05	0	BIPAP	166	110	62	892.7	29.19	69.7	0.419	34.34	14.92	-8	-10	0	1.37	1.68	0.956	2	AUTO	154	98	97	197	52.16	47.3	1.1	11.89	0.2217	-4
3	158	90	101	253.4	27.51	72.51	0.349	10.48	0.359	-6	-8	10	1.15	1.5	1.06	1	FIX	140	110	83	586.9	82.2	18.6	4.412	14.22	0	0	-14	4	1.149	1.78	1.055	2	AUTO	130	100	86	336	58.14	42.3	1.38	8.161	0	4
4	138	86	88	54.79	41.26	57.64	0.716	9.857	0.161	-12	-6	4	1.21	1.35	1.063	1	FIX	148	92	80	1725	24.23	65.9	0.368	46.42	0.4386	-2	2	10	1.06	1.25	1	2	AUTO	114	90	76	1030	66.06	30.9	2.14	14.99	0.2577	20
5	140	80	64	572.5	64.17	36.39	1.763	22.61	2.66	-20	-6	2	1.308	1.375	1.05	2	AUTO	120	80	70	1944	47.02	52.7	0.893	31.84	11.4	6	4	10	1.28	1.27	1.08	0	FIX	140	80	74	305	58.02	42.1	1.38	8.759	0	-10
6	140	90	90	137.5	52.62	50.51	1.042	4.792	0	-12	-8	10	1.25	1.33	1.066	0	AUTO	138	98	82	708.9	51.6	36.7	1.406	24.71	4.147	-4	-2	0	1.425	1.66	1.0625	1	FIX	124	84	80	740	68.62	34.5	1.99	17.2	1.001	-10
7	130	98	80	86.02	64.81	38.84	1.669	4.854	0	-10	-14	6	1.23	1.28	1.06	2	FIX	110	72	90	186.2	77.97	21.6	3.618	7.423	0	-10	-2	26	1.16	1.4	1	2	AUTO	110	90	80	1547	67.76	28.9	2.41	21.38	1.734	-10
8	120	90	72	5395	59.08	42.37	1.394	30.63	11.25	10	6	20	1.39	1.94	1.105	0	AUTO	124	88	70	3723	66.45	34.1	1.949	48.68	19.57	0	2	12	1.32	2.06	1	1	FIX	112	78	62	7066	56.63	42.7	1.33	68.56	35.21	-8
9	156	110	64	4779	59.55	40.86	1.458	37.43	12.93	-40	0	0	1.126	1.21	1.045	2	AUTO	158	104	80	455.8	66.55	34	1.955	12.77	0.4505	4	6	10	1.052	1.25	1.055	1	FIX	152	190	78	292	64.4	36.4	1.77	13.82	0.7229	0
10	120	80	70	103.3	51.68	47.43	1.09	5.805	0	10	10	10	1.157	1.25	1.05	1	FIX	140	86	74	532	76.51	25.5	2.999	8.646	0.2597	-6	0	2	1.04	1.41	1	2	AUTO	140	80	80	484	33.14	66.6	0.5	14.39	0	-12
11	136	90	80	796.8	49.14	48.39	1.015	21.41	1.872	-6	-10	6	1.186	1.26	1.04	2	AUTO	118	74	72	1051	51.81	49.2	1.053	34.94	12.74	-6	-2	4	1.17	1.66	1.05	2	FIX	130	100	74	2444	56.23	43	1.31	39.7	20.25	0
12	148	98	76	242	42.92	55.89	0.768	10.41	0.216	-8	-8	-4	1.12	1.22	1	2	AUTO	118	82	74	800.7	58.05	40.8	1.422	13.18	0	2	-4	0	1.09	1.69	1	2	FIX	124	70	69	404	87.33	18.6	4.71	9.018	0	-4
13	140	94	70	210.4	64.75	35.37	1.83	16.23	1.306	6	4	14	1.23	1.69	1.066	0	FIX	118	90	84	1870	53.52	45.4	1.18	44.69	13.56	-6	-2	4	1.34	2.07	1.09	1	AUTO	120	84	76	880	67.67	31.3	2.16	22.34	2.122	0
14	124	82	72	231.7	76.47	23.22	3.294	9.738	0	-4	-4	4	1.25	1.43	1.052	1	AUTO	122	76	72	383.4	43.13	56.3	0.766	19.52	0.2874	-2	-4	6	1.35	1.81	1.047	1	FIX	120	60	67	1409	56.8	42.4	1.34	22.17	1.437	-2
15	130	90	78	366.6	84.14	17.23	4.884	5.212	0	2	-2	4	1.312	1.285	1	2	AUTO	130	76	82	621.1	89.73	11.7	7.692	5.262	0	-7	6	14	1.17	1.2	1	2	FIX	110	76	82	231	81.35	19.4	4.2	6.698	0	2
16	148	78	74	4796	79.23	21.04	3.766	47.95	26.82	-26	-2	26	1.21	1.75	1.15	1	FIX	134	88	74	3466	53.23	46.5	1.145	41.58	24.29	-4	-16	0	1.3	1.81	1	2	AUTO	140	80	68	1795	18.3	81.8	0.22	39.72	22.73	-4
17	158	102	88	1561	80.23	22.7	3.534	21.06	4.545	-2	-4	2	1.08	1.23	1.055	2	AUTO	130	80	69	674.7	67.33	29.6	2.275	19.36	0.558	0	0	6	1.15	1.35	1.09	2	FIX	120	80	72	1629	58.27	33.4	1.74	25.79	4.134	0
18	158	104	70	675.2	69.51	30.1	2.31	17.88	0.849	-4	0	10	1.15	1.2	1	2	AUTO	160	110	68	3387	68.16	31.3	2.18	28.11	8.564	0	-2	24	1.38	1.667	1.047	0	FIX	170	130	62	1733	68.65	31.1	2.21	24.67	5.817	0
19	156	122	86	594.9	72.12	28.09	2.567	16.58	0.478	-18	-4	20	1.163	2.07	1	2	FIX	130	90	82	157.8	57.62	38.7	1.49	16.35	1.279	4	10	18	1.16	2.07	0.944	2	AUTO	142	110	81	341	55.87	43.9	1.27	14.86	0	-4
20	162	96	77	698.7	69.42	30.41	2.28	12.91	0	-8	0	16	1.17	1.43	1	2	BIPAP	152	98	74	197.5	64.51	36	1.79	12.93	0.37	4	2	20	1.38	1.27	1.06	0	AUTO	146	92	81	126	66.43	33.4	1.99	7.48	0	2
21	176	116	85	473.2	87.86	10.46	8.4	11.58	0	-26	-2	4	1.12	1.25	1	2	AUTO	150	110	78	1113	86.62	14	6.192	20.93	0.99	-6	-10	18	1.34	1.43	1	2	FIX	130	80	74	1385	90.05	8.97	10	23.41	0.9926	0
22	160	98	70	1278	42.79	55.97	0.764	20.73	0	0	2	8	1.18	1.25	1.05	2	AUTO	120	70	66	782.1	63.7	36.7	0.576	24.99	2.959	-6	-2	8	1.21	1.41	0.956	2	FIX	140	90	54	370	7.445	91.2	0.08	26.39	1.799	-4
23	112	60	98	600.8	55.38	44.48	1.245	11.95	0	4	6	10	1.26	1.76	0.89	1	BIPAP	124	78	92	65.16	45.07	53.7	0.84	6.531	0	-8	-4	2	1.089	1.428	1.125	2	AUTO	130	70	86	926	65.97	33.6	1.96	14.76	0.3916	-10
24	132	88	79	532.8	74.08	22.52	3.29	21.82	3.044	-2	2	12	1	1.312	1.166	1	FPAP	128	82	64	580	55.29	44.8	1.234	14.3	0	-6	2	18	1.14	1.43	1	2	AUTO	130	80	71	971	70.51	29.1	2.43	12.28	0	-10
25	146	96	82	3101	37.61	47.15	0.797	29.32	2.61	0	12	20	1.38	2.18	1.06	0	AUTO	150	100	80	864.6	64.51	36	1.79	12.93	0.37	8	22	12	1.32	2.15	1	1	FIX	150	92	86	582	53.09	36.4	1.46	18.46	1.354	0
26	144	94	76	2794	29.3	64.9	0.45	15.22	0	6	2	20	1.13	1.33	0.94	2	AUTO	130	84	78	1691	68.24	31.4	2.175	18.73	1.129	-6	6	14	1.14	1.29	1.05	1	FIX	134	92	74	712	46.99	52	0.91	11.86	0	-10
27	164	112	90	231.6	68.19	33.82	2.016	12.85	0.197	6	2	8	1.44	1.5	0.94	2	AUTO	170	116	90	1078	34.28	55.8	0.614	31.33	1.13	2	2	10	1.09	1.35	1.045	1	FIX	154	96	86	198	73.86	25.1	2.94	10.1	0	-8
28	150	90	74	383.3	50.95	49.96	1.02	10.06	0	-10	0	0	1.057	1.69	1.062	2	AUTO	124	68	75	427.7	74.12	25.5	2.91	10.5	0	-4	-4	2	1.047	1.533	1.058	2	FIX	120	84	74	1397	10.9	75.3	0.14	46.32	0.7614	-2
29	130	78	76	223.6	44.95	54.26	0.828	6.741	0	-10	-8	10	1.09	1.2	1.047	2	AUTO	104	80	74	153	66.74	36.8	1.815	7.199	0	0	0	2	1.09	1.27	0.95	2	FIX	124	84	70	415	69.66	31.8	2.19	11.66	0.285	5
30	144	82	66	417.7	75.68	25.61	2.955	26.91	4.61	-20	-4	-8	1.323	1.8	1.05	2	AUTO	136	76	72	3487	43.13	56.3	0.766	19.52	0.2874	-2	-4	6	1.35	1.81	1.047	1	FIX	130	72	64	4022	56.8	42.4	1.34	22.17	1.437	-2

THERAPY						POLYSONOGRAPHY			COMPLIANCE DATA																QUESTIONAIRES									
	ISOMETRIC EXERCI	DEEP BREATHING TEST	VALSALVA MANOEUVR	POSTURAL TEST	AFT TOTAL	TITRATION STUDY			FPAP						APAP								ESS			FSS			PSQI			CPAP QUESTIONNAIRE	
DBP	DBP					AHI	TYPE OF MASK	PRESSURE	LAST 2WK			TOTAL 4WK			LAST 2 WK				TOTAL 4 WK				BASELINE	AFTER 1st THERAPY	AFTER 2nd THERAY	BASELINE	AFTER 1st THERAPY	AFTER 2nd THERAY	BASELINE	AFTER 1st THERAPY	AFTER 2nd THERAY	AFTER FPAP	AFTER APAP
-6	-10	1.09	1.63	0.9	2	118.3	AIRFIT F20 M	23/17	78	5:20	8	80	5:31	7	81	5:19	15	3.9	80	5:23	15	3.7	24	4	4	42	22	20	2	8	3	20	21
-8	8	1.22	1.18	1	2	74.2	FULL FACE (M)	23/18	71	5:03	3.7	73	5:09	4.2	73	4:53	12	0.9	80	5:28	12	1.5	12	8	8	32	29	24	10	5	3	19	10
4	10	1.125	1.2	1.067	1	71.8	N20 NASAL MEDIUM	15	70	7:10	0.5	70	7:21	1.5	100	7:19	12	2.4	96	7:07	12	2.4	9	3	2	20	14	11	10	6	6	6	7
0	6	1.117	1.29	1.052	2	102.3	FULL FACE COMFORT GEL	25/18	70	4:44	1.4	78	5:23	1	71	4:35	12	0.9	84	5:25	12	0.5	4	5	4	18	15	14	4	3	4	8	8
-10	10	1.3	1.37	1	2	61	FULL FACE(M)	9	70	4:26	0.5	73	4:41	0.5	73	5:22	11	1	90	6:22	11	1.1	22	12	17	46	43	59	11	6	6	13	18
6	8	1.42	1.4	0.944	2	36.4	N20 NASAL LARGE	14	70	4:24	0.3	73	5:24	0.3	57	4:21	8	0.9	80	5:59	8	0.9	5	2	2	32	33	27	5	3	2	12	24
0	6	1.23	1.22	1.05	1	66.8	COMFORTGEL NASAL (S/M)	9	92	6:47	0.4	89	6:29	0.7	93	6:50	9.2	0.7	93	7:00	8.9	0.7	9	7	8	48	46	44	12	5	6	12	12
0	10	1.342	2.125	0.904	1	105.4	COMFORTGEL NASAL (L)	14	70	5:47	0.8	70	5:28	0.8	85	5:33	8.8	1.1	80	5:37	8.9	1.1	15	10	6	25	25	21	10	5	5	16	18
16	32	1.1	1.43	1.05	1	102.9	COMFORTGEL NASAL (S/M)	15	70	4:00	0.7	70	4:01	0.8	80	4:59	8.3	1.8	70	4:28	8.3	1.8	20	7	9	33	12	16	6	3	4	43	34
0	20	1.119	1.43	1	2	54.7	FULL FACE	13	100	7:02	5.1	100	7:10	4.1	100	7:08	14	3.4	93	6:15	16	4.5	8	9	17	22	17	17	5	5	6	23	25
8	10	1.26	1.38	0.95	1	57.7	N20 NASAL MEDIUM	12	85	5:58	0.7	70	5:12	0.6	92	6:48	8.2	0.7	88	6:39	8.3	0.8	6	5	2	45	32	52	13	7	6	12	10
4	12	1.043	1.411	0.954	2	103.7	N20 NASAL MEDIUM	16	85	6:01	0.6	88	5:45	0.5	71	4:55	14	0.8	76	5:20	14	0.6	11	4	3	44	30	30	4	4	4	10	15
6	16	1.421	1.6	1	1	21.7	FULL FACE	16	78	5:27	1.8	70	4:05	1.8	71	5:17	14	2.9	73	5:04	13	2.4	4	0	0	9	9	9	6	4	4	15	15
0	2	1.309	1.55	1.04	1	23.8	N20 NASAL MEDIUM	7	86	6:18	0.7	90	6:29	0.7	80	5:30	7	1.2	80	5:19	6.8	1	12	9	4	39	31	44	7	7	8	18	8
4	14	1.103	1.4	1.055	1	37	FULL FACE	12	92	7:01	3.1	74	5:35	3	100	6:43	10	5.9	70	4:26	10	5.7	2	2	2	44	30	9	4	3	5	9	7
-4	4	1.24	2.13	0.958	2	33.2	N20 NASAL MEDIUM	11	71	4:00	0	80	4:46	0	92	5:44	9.2	0	96	5:52	9.3	0.1	7	3	3	62	50	42	10	5	7	28	14
0	10	1.13	1.29	0.95	2	116	N20 NASAL MEDIUM	13	85	5:16	1	85	5:49	0.8	92	6:01	13	0.8	90	5:55	13	0.8	24	7	0	48	24	24	13	6	8	25	6
-10	2	1.154	1.647	1.22	2	51	N20 NASAL MEDIUM	10	78	5:05	0.4	70	4:22	0.5	86	5:36	6.1	0.5	70	4:00	6.1	0.4	6	0	5	63	58	60	5	5	8	20	24
0	20	1.24	1.5	1	1	34.6	N20 NASAL MEDIUM	10	78	6:10	0.1	70	5:04	0.2	80	6:21	7.7	0.1	70	5:38	7.7	0.1	11	1	2	29	24	26	4	3	3	14	15
2	20	1.21	1.6	1	1	99.3	FULL FACE LARGE	23/19	74	4:36	1.8	70	4:59	2.2	70	4:46	17	2.6	72	5:08	17	2.5	14	9	1	20	18	17	7	4	5	14	10
8	30	1.41	1.37	1.25	0	92	N20 NASAL MEDIUM	13	78	7:35	0.7	83	8:08	0.7	85	6.3	12	1.3	82	5.5	12	1.2	16	0	1	60	25	35	8	6	7	6	7
-2	8	1.27	1.5	1.038	1	22	N20 NASAL MEDIUM	6	70	5:20	1.8	70	5:09	1.8	70	4:29	9.7	1.7	70	4:11	9.4	1.3	3	0	0	44	17	16	7	5	3	60	40
0	6	1.15	1.35	0.947	2	94.8	FULL FACE LARGE	20/14	80	5:28	0.4	70	4:22	0.4	87	6:40	10	1.2	84	6:23	10	1.1	13	6	7	34	21	21	14	8	7	7	9
6	10	1.15	1.43	1	2	33.6	N20 NASAL MEDIUM	10	93	5:39	0.8	92	5:32	0.8	70	4:00	11	0.9	75	4:32	11	0.8	12	1	8	63	36	60	13	7	14	10	20
0	8	1.26	1.46	1	2	31.6	N20 NASAL MEDIUM	7	86	5:25	1.1	79	5:12	0.6	93	6:55	8.9	0.6	90	6:35	8.8	0.6	15	5	5	16	9	10	16	10	10	7	6
0	10	1.21	1.28	0.9	1	101.8	N20 NASAL MEDIUM	9	100	6:35	0.5	100	6:33	0.5	100	6:35	7.5	0.5	100	6:33	7.2	0.5	10	2	1	12	6	6	11	9	6	10	14
-2	2	1.142	1.33	1	2	15.9	N20 NASAL MEDIUM	7	93	7:36	0.8	70	4:02	0.8	70	4:20	8.2	0.9	70	4:02	7.2	0.7	12	11	9	15	14	12	14	12	13	14	24
6	6	1.139	1.35	1	2	34	N20 NASAL MEDIUM	14	70	4:02	0.6	70	4:01	0.5	70	4:00	12	0.6	70	4:17	11	1.1	17	7	0	35	23	9	9	4	5	29	12
4	10	1.09	1.33	1.045	1	27.3	N20 NASAL MEDIUM	6	78	6:25	1.1	91	6:23	1.1	85	7:59	9.7	0.8	85	7:59	9.7	0.8	16	11	4	33	51	26	10	5	5	9	15
0	2	1.309	1.55	1.04	1	87	N20 NASAL LARGE	7	90	6:22	1.1	75	4:45	0.5	75	5:06	7	0.8	81	5:17	6.7	0.6	10	1	9	57	14	38	6	5	4	9	9